JOC The Journal of Organic Chemistry

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C−H Bond Functionalization via Hydride Transfer: Formation of α-Arylated Piperidines and 1,2,3,4-Tetrahydroisoquinolines via Stereoselective Intramolecular Amination of Benzylic C−H Bonds

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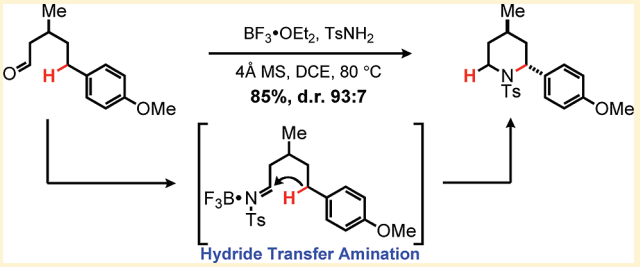
Supporting Information

ABSTRACT: We here report a study of the intramolecular amination of sp^3 C−H bonds via the hydride transfer cyclization of *N*-tosylimines (HT-amination). In this transformation, 5-aryl aldehydes are subjected to *N*-toluenesulfonamide in the presence of $BF_3{\cdot}OEt_2$ to effect imine formation and HT-cyclization, leading to 2-arylpiperidines and 3-aryl-1,2,3,4-tetrahydroisoquinolines in a one-pot procedure. We examined the reactivity of a range of aldehyde substrates as a function of their conformational flexibility. Substrates of higher conformational rigidity were more reactive, giving higher yields of the desired products. However, a single substituent on the alkyl chain linking the *N*-tosylimine and the benzylic sp^3 C−H bonds was sufficient for HT-cyclization to occur. In addition, an examination of various arenes revealed that the electronic character of the hydridic C−H bonds dramatically affects the efficiency of the reaction. We also found that this transformation is highly stereoselective; 2-substituted aldehydes yield *cis*-2,5-disubstituted piperidines, while 3-substituted aldehydes afford *trans*-2,4-disubstituted piperidines. The stereoselectivity is a consequence of thermodynamic control. The pseudoallylic strain between the arene and tosyl group on the piperidine ring is proposed to rationalize the greater stability of the isomer with the aryl ring in the axial position. This preferential placement of the arene is proposed to affect the observed stereoselectivity.



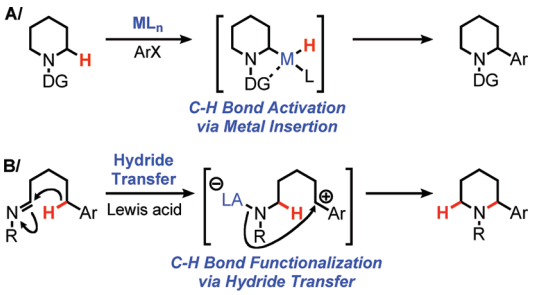
INTRODUCTION

C−H bond functionalization represents a process of broad synthetic potential owing to the ubiquity of C−H bonds in organic compounds.[1] As part of a broad program aimed at the development of new approaches for the direct functionalization of C−H bonds, we have been interested in the design of new methods for the synthesis of arylated pyrrolidines and piperidines.[2,3] The wide ranging biological activity of such compounds has granted them an important status in the fields of organic and medicinal chemistry.[4]

To complement approaches initiated by transition-metal insertion into C−H bonds[2] and those relying on an external oxidant,[3] for preparation of α-arylpiperidines we considered an alternative mode of reactivity based on the hydride-transfer cyclization of imines (HT-amination, Scheme 1B).[5] This approach is based on a Lewis acid promoted hydride transfer to an activated imine, followed by C−N bond formation. We have previously demonstrated that the HT-cyclization effects the coupling of a range of hydride acceptors, such as aldehydes, enones, enals, vinyl acetals, and unactivated alkynes, with sp^3 C−H bonds to deliver a diverse array of complex structural scaffolds, under mild conditions (Figure 1).[6] HT-cyclization has since become an active area of research, which has led to the development of a number of interesting transformations.[7−12]

In regard to HT-amination reactions, an early report by Reinhoudt et al. describes the thermal-cyclization of *o*-aminobenzaldimines of type **I** to aminals **II** (Scheme 2A).[13]

Scheme 1. Two Complementary Approaches to α-Arylated Piperidines via C−H Bond Functionalization[a]



[a]DG = directing group.

More recently, the research teams of Seidel[14a] and Akiyama[14b] showed that triflic acid catalyzed this transformation, leading to expansion of its scope and utility. Both the thermal and the acid-catalyzed reactions of aromatic imines can be rationalized by a sigmatropic hydrogen shift. However, a through-space hydride transfer mechanism is also reasonable. In the context of saturated substrates (where a through-space hydride transfer is the only reasonable mechanistic rationale), Tietze and colleagues have reported the HT-cyclization of imines within

Received: March 27, 2012
Published: June 6, 2012

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

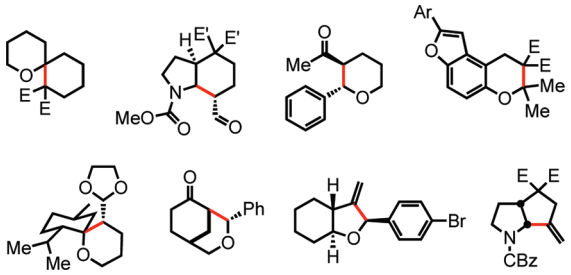
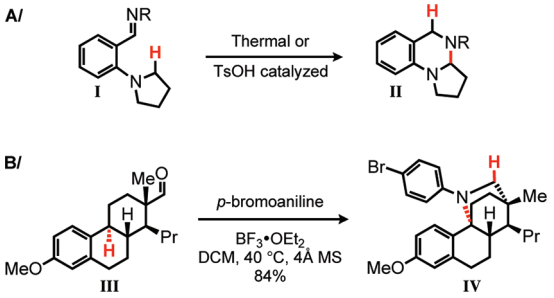


Figure 1. Examples of diverse structures prepared by HT-cyclization in our group. The bond formed during the process is highlighted in red. E = CO_2Me, E′ = CO_2Et, Ar = 4-$MeOC_6H_4$.

Scheme 2. Formation of Cyclic Amines via the HT-cyclization of Imines



conformationally rigid steroidal substrates, giving access to complex isoquinuclidines of type **IV** (Scheme 2B).[15] This reaction has recently been expanded to the corresponding oximes and hydrozones.[16]

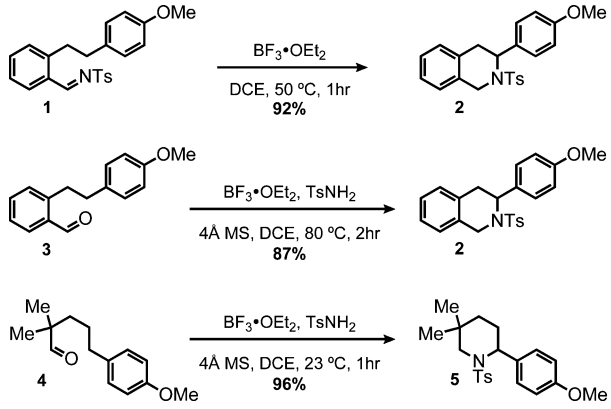
In this study, we examined the importance of conformational rigidity for the HT-cyclization of imines in a systematic manner. We explored the reactivity of aldehyde substrates with varying degrees of conformational freedom, ranging from rigid aromatic aldehydes to entirely unrestricted 5-arylpentanals. We found that a single substituent on the alkyl chain connecting the *N*-tosylimine (formed in situ from the aldehyde) and the benzylic group is sufficient for an efficient HT-cyclization to occur. Furthermore, we discovered that the HT-cyclization is highly stereoselective, and we provide a mechanistic rationale for the observed results.

RESULTS AND DISCUSSION

Initial Investigation of the HT-amination: One-Pot Protocol. We first examined the aromatic *N*-tosylimine substrate **1** considering the restricted conformational freedom imparted by the aromatic core, which forces the hydride acceptor (*N*-tosylimine) and the hydride donor (the benzylic C−H bonds) into proximity and thereby should facilitate the hydride transfer (Scheme 3). Moreover, substrates of type **1** are readily accessible from commercially available materials and provide a direct route to an attractive but medicinally underexplored heterocyclic motif, the 3-aryl-1,2,3,4-tetrahydroisoquinoline (also see discussion below).

Substrate **1** was subjected to $BF_3{\cdot}OEt_2$ (2 equiv) in DCE at 50 °C, and we were gratified to observe an efficient conversion to the *N*-tosyl-1,2,3,4-tetrahydroisoquinoline **2** in 92% yield (Scheme 3). As $BF_3{\cdot}OEt_2$ is known to promote the condensation of aldehydes and *N*-toluenesulfonamide, we subjected the precursor aldehyde **3** to $BF_3{\cdot}OEt_2$ (3 equiv), *N*-toluenesulfonamide (2 equiv) and 4 Å molecular sieves (MS).[17]

Scheme 3. One-Pot Condensation/HT-amination Protocol



After heating at 80 °C for 2 h, 1,2,3,4-tetrahydroisoquinoline **2** was isolated in 87% yield. Lewis acid optimization revealed that $BF_3{\cdot}OEt_2$ and TiF_4 were the only reagents capable of promoting complete conversion of aldehyde **3** to product **2** (see Table S1 in the Supporting Information for an extensive screen). We also investigated the use of alternative amines in a one-pot procedure with substrate **3**. While aniline gave complex product mixtures, 4-nitrobenzenesulfonamide led to a clean reaction mixture. However, the rate of reaction was dramatically slower than that with *N*-toluenesulfonamide, and incomplete conversion of the aldehyde to the imine was a recurring problem.

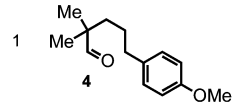
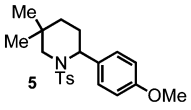
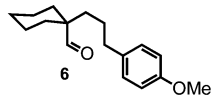
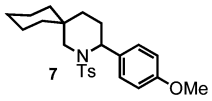
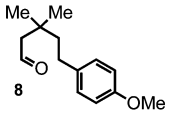
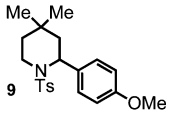
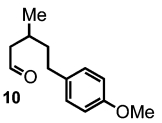
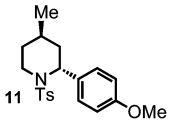
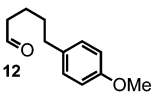
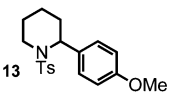
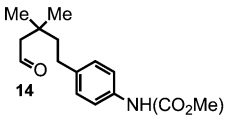
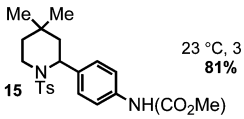
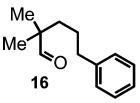
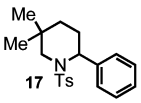
With the one-pot procedure in hand, we next directed our attention toward aliphatic aldehyde substrates, which upon HT-amination would yield α-arylated piperidines (Scheme 3). Our investigation began with aldehyde **4**, containing *gem*-dimethyl substitution in the α-position, to promote the intramolecular hydride transfer by increasing the rigidity of the substrate and preventing the potential tautomerization of the imine to the enamine. This substrate gave the *2-aryl-piperidine* **5** *in 96% yield at room temperature in 1 h, the result that stimulated the systematic examination of the aliphatic substrates.* Attempts to extend the HT-amination reactivity to ketone substrates of both the aryl and aliphatic classes were unsuccessful, with complete recovery of the starting ketone observed in all cases.

HT-amination of Aliphatic Aldehydes: Conformational Rigidity of the Substrate Backbone and Electronics of the Benzylic C−H Bonds. Preliminary studies outlined above established that aliphatic aldehyde **4** exhibits high reactivity in the one-pot HT-cyclization protocol. Similarly, the cyclic aldehyde **6** afforded an excellent yield of spirocyclic piperidine **7** under mild reaction conditions (Table 1, entry 2). Moving the *gem*-dimethyl substitution in the β-position had no major effect; substrate **8** furnished the corresponding product **9** in 95% yield under the same conditions (Table 1, entry 3).

We next examined substrate **10**, containing one methyl group in the β-position, and substrate **12**, containing no substitution on the alkyl linker (Table 1, entries 4 and 5). Importantly, both substrates afforded the corresponding products, demonstrating the feasibility of HT-amination of aliphatic substrates with a small conformational bias, albeit with significantly lower yield. The efficiency of the HT-cyclization was improved by optimization of reaction conditions as is described in the following section (Table 2). Unfortunately, even under the optimized conditions unsubstituted substrate **12** failed to

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

Table 1. HT-amination Scope: Conformational Rigidity and Electronics of Aldehyde Substrates[a]

entry	substrate	product	conditions/yield
1			23 °C, 1 hr **96%**
2			23 °C, 1 hr **98%**
3			23 °C, 1 hr **95%**
4			23 °C, 80 min **35%**[b]
5[c]			100 °C, 8 hr **30%**
6			23 °C, 3 hr **81%**
7[c]			100 °C, 18 hr **32%**

[a]Reactions performed at 0.05 M in dry DCE, with 2 equiv of $TsNH_2$, 3 equiv of $BF_3{\cdot}OEt_2$ and 4 Å MS 200% by wt [b]Obtained as a 95:5 *trans*/*cis* mixture. [c]Reactions run in a sealed vial.

furnish the desired product in higher yield. We also considered the incorporation of a heteroatom into the alkyl linker, which upon HT-amination would afford morpholine and piperazine products. However, we have found that the presence of a heteroatom in the backbone of various HT-cyclization substrates is generally not tolerated and leads to decomposition of the starting material.

In the context of these substrates, we also explored the effect of electronics of the benzylic C–H bonds and the arene ring. In addition to the methoxy group, the carbamate-containing substrate **14** provided 81% yield of product **15** (Table 1, entry 6). In addition, we were glad to find that substrate **16** with an unsubstituted phenyl ring undergoes the cyclization, although with lower efficiency (Table 1, entry 7). As expected, electron-donating substituents are required to achieve high yields of the desired products. This is a limitation pertinent to all HT-cyclization reactions as the stabilization of the carbocation intermediate, formed by the hydride transfer, is required (Scheme 1B).

HT-amination of Aliphatic Aldehydes is Highly Stereoselective. Examining the reactivity of substrate **10**, bearing one methyl group in the β-position, revealed that the HT-cyclization is stereoselective (Scheme 4A). Optimization of the reaction conditions revealed that elevating the temperature to 80 °C and decreasing the substrate concentration (to disfavor formation of side products stemming from intermolecular reactions) led to a substantial improvement of the reaction efficiency, from 37% to 85% yield (Table 2).

Scheme 4. HT-amination Is Stereoselective

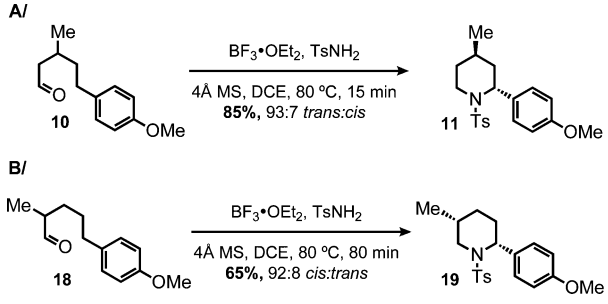
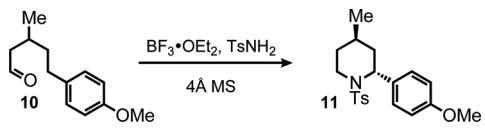


Table 2. Optimization of the HT-Amination Protocol for Monosubstituted Substrates[a]



entry	solvent	conc (M)	$BF_3{\cdot}OEt_2$ (equiv)	*T* (°C)	time	yield (%)	*trans*/*cis*[b]
1	DCE	0.05	3	23	80 min	37	95:5
2	DCE	0.025	3	23	80 min	46	95:5
3	DCE	0.012	3	23	80 min	70	94:6
4	DCE	0.006	3	23	80 min	70	90:10
5	DCM	0.012	3	23	100 min	55	95:5
6	toluene	0.012	3	23	100 min	50	95:5
7	MeCN	0.012	3	23	19 h	7	95:5
8	THF	0.012	3	23	10 h	0	
9	**DCE**	**0.012**	**3**	**80**	**15 min**	**85**	**93:7**
10	DCE	0.012	2	80	30 min	80	93:7
11	DCE	0.012	1	80	30 min	81	92:8
12	DCE	0.012	0.5	80	30 min	85	92:8
13[c]	DCE	0.012	0.5	80	150 min	84	95:5

[a]2 equiv of $TsNH_2$ employed, unless otherwise noted. [b]Ratio determined by ^1H NMR of the crude reaction. [c]1.1 equiv of $TsNH_2$ employed.

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689–6702

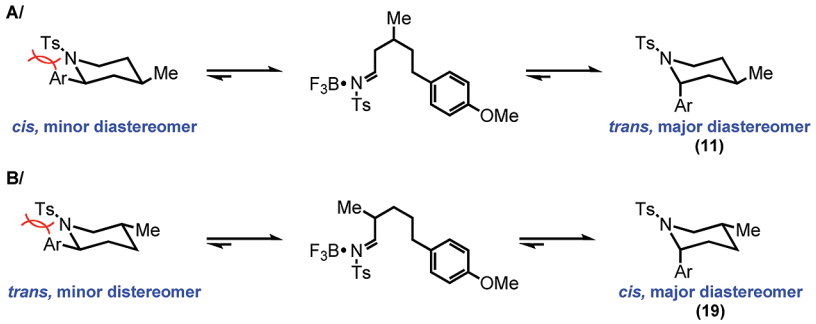


Figure 2. Mechanistic rationale for the observed diastereoselectivity. (A) The experimental data supports the thermodynamic control of the stereoselectivity. The stereoisomer with the α-aryl group in the axial position is more stable due to the steric bulk of the *N*-tosyl group and its position on a partially sp^2-hybridized nitrogen. (B) The same rationale explains the formation of the *cis*-isomer of 2,5-disubstituted piperidine **19** as the major product.

Modification of reaction conditions during optimization had a small effect on the diastereoselectivity.

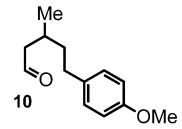
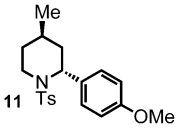
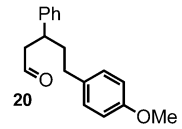
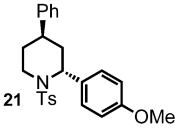
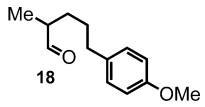
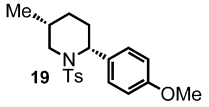
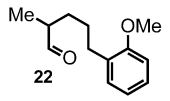
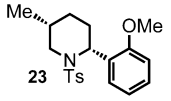
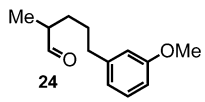
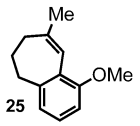
Under optimized conditions (Table 2, entry 9), aldehyde **10** afforded two diastereoisomers in a 93:7 ratio as determined by ^{1}H NMR of the crude mixture (Scheme 4A). The geometry of the major *trans*-isomer was established by X-ray crystallography (see the Supporting Information). However, aldehyde **18** with the methyl group in the α-position afforded 2,5-disubstituted piperidine **19** in 65% yield and high stereoselectivity favoring the *cis*-isomer (dr 92:8, Scheme 4B). The structure and geometry of the major isomer was again confirmed by X-ray crystallographic analysis (see the Supporting Information). As expected, substantial racemization occurs under the HT-amination conditions when optically pure substrate **18** is used (see the Supporting Information).

While we did observe similar results with a substoichiometric amount of $BF_3{\cdot}OEt_2$ (0.5 equiv, entries 12 and 13, Table 2), these reaction conditions were not general and failed to effect the HT-amination of other substrates in good yield.

Mechanistic Rationale for the Observed Stereoselectivity. To determine whether the diastereoselectivity of the HT-amination is kinetically or thermodynamically driven, a mixture of isomers **11** enriched in the minor *cis*-isomer (63:37 *trans*/*cis* ratio)[18] was subjected to the reaction conditions (Figure 2). The result was a shift in the ratio to 90:10 *trans*/*cis*, which is very close to the product ratio found in the cyclization reaction. Similar results were obtained for the 2,5-disubstituted piperidines **19** when a 72:28 *cis*/*trans* ratio of products was equilibrated under the reaction conditions to a 92:8 *cis*/*trans* mixture. These results demonstrate the reversibility of the cyclization step and support thermodynamic control as the source of the observed high stereoselectivity. In both cases (Figure 2A,B), the aryl ring prefers to adopt an axial position in the chair of the piperidine ring to avoid the steric interaction with the sulfonamide group. The propensity for axial preference of substituents adjacent to sp^2-hybridized nitrogens has been termed "pseudo-allylic strain" and has previously been proposed to explain conformation preferences of *N*-acyl- and *N*-sulfonylpiperidines.[19] Under circumstances where the reaction would be controlled kinetically, the same pseudoallylic strain rationale could be invoked in the corresponding transition states.

HT-amination of Monosubstituted Aliphatic Aldehydes: Substrate Scope. As discussed above, substrate **10** containing a methyl group in the β-position gave the *trans*-isomer of **11** in excellent yield and stereoselectivity (Table 3, entry 1). Similarly, compound **20** presenting a β-phenyl ring also reacted well under the optimized conditions, affording the diaryl piperidine **21** with excellent stereoselectivity (dr 92:8 favoring the *trans*-isomer) and modest yield (45%, Table 3, entry 2).

Table 3. Stereoselective HT-amination: Substrate Scope[a]

entry	substrate	product	conditions/yield[b]
1			80 °C, 15 min **85%** *93:7 trans:cis*
2			80 °C, 2 hr **45%** *92:8 trans:cis*
3			80 °C, 80 min **65%** *92:8 cis:trans*
4			80 °C, 6 hr **28%** *73:27 cis:trans*
5			80 °C, 1 hr **90%**

[a]Reactions performed at 0.012 M in dry DCE, with 2 equiv of $TsNH_2$, 3 equiv of $BF_3{\cdot}OEt_2$, and 4 Å MS 200% by wt [b]dr determined by ^{1}H NMR of the crude reaction mixture.

Substrate **18** with the methyl group in the α-position exhibited relatively lower reactivity in comparison to the regioisomeric aldehyde **10** (65% yield, Table 3, entry 3), but the stereoselectivity was high and comparable between these two substrates. The transposition of the methoxy group on the arene to the *ortho*-position resulted in a decrease in yield and diastereoselectivity (28% yield, 73:27 *cis*/*trans*; Table 3, entry 4). Positioning the methoxy group in the *meta*-position disfavored the HT-cyclization and led to bicycle **25**, the product of a Friedel–Crafts hydroxyalkylation followed by dehydration (Table 3, entry 5). We attribute this unexpected result to the decreased stabilization of the ensuing carbocation

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689–6702

by the methoxy group in the *meta*-position, which thereby decreases the hydridic character of the benzylic C−H bonds. In addition, this placement of the methoxy group may deactivate the hydridic C−H bonds via a sigma withdrawing effect. With these effects in action the Friedel−Crafts hydroalkylation pathway dominates, leading to cyclization at the electron rich *ortho*-position of the methoxy group.

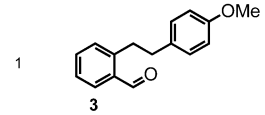
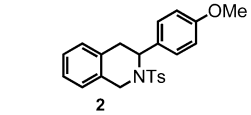
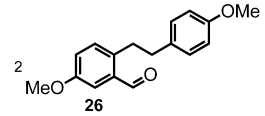
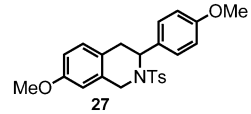
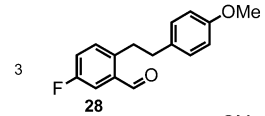
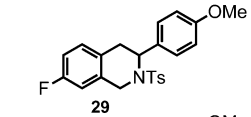
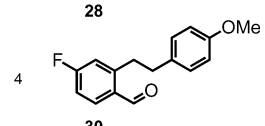
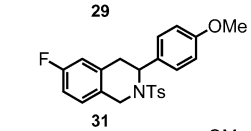
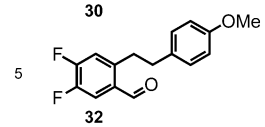
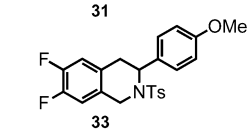
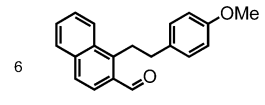
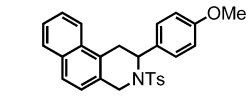
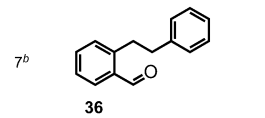
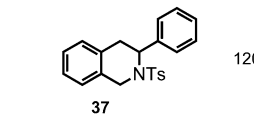
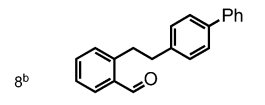
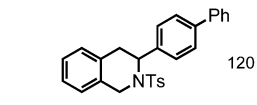
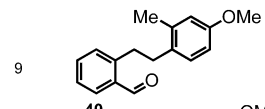
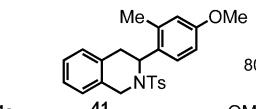
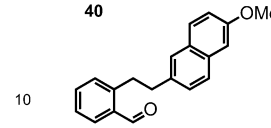
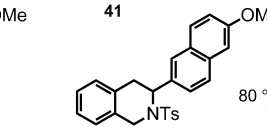
HT-amination of Aromatic Aldehydes: Substrate Scope. We revisited the reactivity of *o*-(2-arylethyl)-benzaldehydes in the HT-amination reaction since they afford an interesting and underexplored class of heterocycles, 3-aryl-1,2,3,4-tetrahydroisoquinolines (Table 4). While there are numerous methods reported in the literature for the synthesis of 1-substituted tetrahydroisoquinolines,[20] there are only a few general methods for the incorporation of the aryl substituents at the 3-position.[5,21] Following our approach based on the HT-cyclization, 3-aryl-1,2,3,4-tetrahydroisoquinolines can be prepared in four steps from commercially available 2-bromobenzaldehydes.

The introduction of either electron-donating (Table 2, entry 2) or -withdrawing groups (Table 2, entries 3−5) onto the benzaldehyde ring (hydride acceptor) was well tolerated. Extension of the π-system of the parent substrate **3** to a naphthaldehyde afforded compound **35** in 85% yield, with an extension of the reaction time to 5 h.

Directing our focus to the hydride donor portion of the substrate, we found that the absence of the *p*-methoxy group again was not tolerated under the standard reaction conditions. While clean conversion to the imine was observed by ^{1}H NMR, only trace HT-amination product **37** was observed even after heating at 120 °C for 72 h. However, a phenyl group in the 4-position was tolerated, giving the biphenyl-substituted product **39** in 46% yield. The elevated reaction temperature of 120 °C was required in order to promote the HT-cyclization. The isolation of pure crystals of **39** permitted an X-ray analysis, thereby affirming the proposed 3-aryl-1,2,3,4-tetrahydroisoquinoline structure of this and all related products (see the Supporting Information). Substrate **40** was prepared in order to investigate the effects of steric hindrance on the HT-amination, given the potential for the *o*-methyl group to impede cyclization. Such a steric effect was found to be minimal, with product **41** being formed in 80% yield. The methoxynaphthalene derivative **42** was also reactive furnishing a 71% yield of product **43** after an extended reaction time of 24 h.

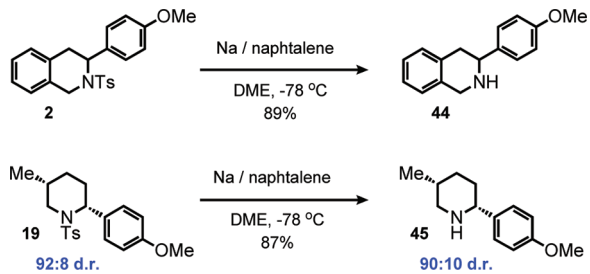
Deprotection of *N*-Tosyl Piperidines. Lastly, we investigated the removal of *N*-tosyl group in the context of the products discussed in this paper, which are all benzylamines. After exploring several known procedures, we found that sodium naphthalenide, prepared fresh in dimethoxyethane (DME) at −78 °C, was effective. For example, compound **2** was deprotected to afford 3-aryl-1,2,3,4-tetrahydroisoquinoline **44** in 89% (Scheme 5).[22] In addition, deprotection of substrate **19** was accomplished in 87% yield with minimal impact on the stereochemical integrity of the product.

Table 4. Synthesis of 3-Aryl-1,2,3,4-tetrahydroisoquinolines via HT-amination[a]

entry	substrate	product	conditions/yield
1	 **3**	 **2**	80 °C, 2 hr **87%**
2	 **26**	 **27**	80 °C, 2 hr **75%**
3	 **28**	 **29**	80 °C, 6 hr **88%**
4	 **30**	 **31**	80 °C, 6 hr **88%**
5	 **32**	 **33**	80 °C, 6 hr **88%**
6	 **34**	 **35**	80 °C, 5 hr **85%**
7[b]	 **36**	 **37**	120 °C, 72 hr **trace**
8[b]	 **38**	 **39**	120 °C, 72 hr **46%**
9	 **40**	 **41**	80 °C, 3 hr **80%**
10	 **42**	 **43**	80 °C, 24 hr **71%**

[a]Reactions performed at 0.05 M in dry DCE, with 2 equiv of $TsNH_2$, 3 equiv of $BF_3{\cdot}OEt_2$, and 4 Å MS 200% by wt [b]Reactions run in a sealed vial.

Scheme 5. Deprotection of the *N*-Tosyl Group



CONCLUSION

In this study, we examined the formation of α-arylpiperidines via HT-cyclization of *N*-tosylimines formed in situ from the corresponding aldehydes. We showed that conformationally rigid aromatic aldehydes are readily converted to 3-aryl-1,2,3,4-tetrahydroisoquinolines, an interesting class of heterocycles. In a systematic manner, we examined the reactivity of aliphatic aldehydes (5-arylpentanals). We found that a single substituent on the alkyl chain connecting the *N*-tosylimine and the benzylic

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

group is sufficient for an efficient HT-cyclization to occur. Furthermore, we discovered that the HT-cyclization of these substrates is highly stereoselective affording stereodefined 2,4- and 2,5-disubstituted piperidines. In addition, we have shown that the HT-cyclization of *N*-tosylimines is a reversible, thermodynamically controlled process and the high stereoselectivity is ascribed to the pseudo-allylic strain between the *N*-tosyl group and the arene ring in the 2-position. This study has served to increase the understanding of the HT-amination reaction and has expanded the scope of HT-transformations in general.

EXPERIMENTAL SECTION

General Considerations. Argon was purified by passage through Drierite. Nuclear magnetic resonance spectra were recorded at 300 K on 300, 400, or 500 MHz NMR spectrometers. ^{1}H NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm). ^{13}C NMR spectra recorded in $CDCl_3$ were referenced to the residual solvent peak (77.16 ppm). High-resolution mass spectra (HRMS) were obtained on a high resolution sector type double focusing mass spectrometer (ionization mode: FAB+). Flash chromatography was performed on silica gel (230−400 mesh). Reactions were monitored by GC or TLC analysis using hexanes/ethyl acetate and hexanes/diethyl ether mixtures as the eluent and visualized using permanganate stain and/or cerric ammonium molybdate stain and/or UV light. Chloroform-d_1 was stored over 4 Å molecular sieves. Dichloroethane and triethylamine were freshly distilled from CaH_2. Substrates **12**[23a] and **36**[23b] were prepared according to literature procedures.

General HT-amination Protocol. Activated 4 Å molecular sieves (200% by wt relative to substrate) were added to an oven-dried flask followed by toluenesulfonamide (2 equiv), the appropriate substrate, and a magnetic stir bar. The mixture was sealed under a rubber septum and backfilled with argon. DCE, freshly distilled from calcium hydride, was then added via syringe, followed by addition of $BF_3{\cdot}OEt_2$ (3 equiv) via microsyringe. The reaction was placed in an oil bath and heated to 80 °C. The reaction was monitored by TLC, employing UV and $KMnO_4$ stain visualization; however, the *N*-tosylimine and cyclized product often exhibited identical R_f values. As such, ^{1}H NMR may be required to ensure the reaction has gone to completion. Following conversion of the starting material, the reaction was filtered through a cotton plug and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel.

Representative Procedure. To a solution of 1-(3-(4-methoxyphenyl)propyl)cyclohexanecarbaldehyde (**6**) (66 mg, 0.3 mmol) in freshly distilled DCE (6 mL) were added $TsNH_2$ (103 mg, 0.6 mmol) and 4 Å molecular sieves (132 mg). The reaction was sealed with a septum under argon. $BF_3{\cdot}OEt_2$ (113 μL, 0.9 mmol) was then added via syringe, and the mixture was stirred at room temperature. The reaction was monitored by TLC (30% Et_2O/Hex). Upon complete consumption of the starting material, the mixture was filtered through a cotton plug and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with 25% Et_2O/Hex to afford 3-(4-methoxyphenyl)-2-tosyl-2-azaspiro[5.5]-undecane (**7**) as a white solid (107 mg, 95%).

General Heck Reaction Protocol. A flame-dried Schlenk tube was charged with $Pd(OAc)_2$ (5 mol %), followed by the addition of DMF (0.25 M). The appropriate alkene (1 equiv) and aryl iodide/bromide (1.1 equiv) were subsequently added. Freshly distilled triethylamine (1.1 equiv) was then added to the reaction mixture. The vessel was equipped with a magnetic stir bar and sealed under argon. The reaction was then heated to 80 °C and monitored by TLC. Upon complete consumption of the alkene, the reaction was cooled to room temperature and poured into water (3 × volume of DMF). The resulting solution was extracted with EtOAc (4 × volume of DMF). The combined organic layers were then washed twice with water and once with brine and dried over $MgSO_4$. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was then chromatographed on silica gel to afford the pure product.

General Sonogashira Coupling Protocol. A flame-dried flask was charged with $PdCl_2(PPh_3)_2$ (2.5 mol %) and CuI (2.5 mol %). Freshly distilled triethylamine (0.25 M) was then added followed by the appropriate aryl bromide (1 equiv) and alkyne (1.1 equiv). The reaction was sealed under argon and heated to 50 °C. The reaction was monitored by TLC. Upon consumption of the aryl bromide, the mixture was cooled to room temperature and concentrated in vacuo. The residue was then dissolved in EtOAc and washed with water and NH_4Cl (aq satd). The organic layer was then dried over $MgSO_4$. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel to afford the pure product.

General Alkene/Alkyne Hydrogenation Protocol. To a solution of the appropriate alkene or alkyne in EtOH (0.4 M) was added 10% by wt Pd/C (20% by wt relative to alkyne/alkene). The flask was equipped with a magnetic stir bar, and the suspension was sealed with a septum under an atmosphere of H_2 supplied via a balloon. The reaction was stirred vigorously and monitored by ^{1}H NMR. Following complete hydrogenation, the suspension was filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford the product; the crude product was typically pure by ^{1}H NMR and employed directly in the next step.

General $LiAlH_4$ Reduction Protocol. A flame-dried flask was charged with $LiAlH_4$ (1.5 equiv), followed by the addition of THF (0.17 M based on ester). The suspension was then cooled to 0 °C in an ice bath, and a solution of the appropriate ester in THF (0.24 M based on ester) was added slowly. The reaction was then allowed to warm to room temperature. The reaction was monitored by TLC. After complete reduction of the starting material, the reaction was cooled to 0 °C and quenched with water (3 mL/1 g $LiAlH_4$), KOH 20% (9 mL/1 g $LiAlH_4$), and finally water (15 mL/1 g $LiAlH_4$). After being stirred for 5 min, the suspension was filtered and the filtrate dried over $MgSO_4$ and concentrated in vacuo. The product alcohol was typically pure by ^{1}H NMR and employed directly in the next step.

General MnO_2 Oxidation Protocol. To a solution of alcohol (1 equiv) in DCM (0.3 M) was added MnO_2 (5 equiv). The suspension was stirred vigorously and monitored by TLC. Upon complete conversion of the starting material, the mixture was filtered through Celite and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel to afford the pure aldehyde.

General Pyridinium Chlorochromate (PCC) Oxidation Protocol. To a solution of alcohol (1 equiv) in DCM (0.2 M) was added PCC (2.25 equiv). The mixture was stirred and monitored by TLC. Upon conversion of the starting material, the suspension was filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue chromatographed on silica gel to afford the pure aldehyde.

General Swern Oxidation Protocol. A solution of DMSO (2.4 equiv) in dry DCM (1 M) was cooled to −78 °C under an argon atmosphere. Oxalyl chloride (1.2 equiv, 2.0 M solution in DCM) was added dropwise. The resulting solution was stirred at −78 °C for 30 min. A solution of the corresponding alcohol (1 equiv) in dry DCM (5 M) was added dropwise to the reaction mixture. The reaction was stirred at −78 °C for 1 h. Triethylamine was then added to the solution, and the mixture was allowed to warm to room temperature. The reaction mixture was poured into water (3 × total volume of DCM) and extracted four times with DCM. The combined organic layers were then washed sequentially with saturated aqueous $CuSO_4$ solution and brine and then dried over $MgSO_4$. The suspension was filtered and the filtrate concentrated in vacuo. The residue was then chromatographed on silica gel to afford the pure aldehyde.

***N*-(2-(4-Methoxyphenethyl)benzylidene)-4-methylbenzenesulfonamide (1).** To a solution of 2-(4-methoxyphenethyl)-benzaldehyde[24] (720 mg, 6.0 mmol) in THF (6 mL) were added $TsNH_2$ (1.03 g, 6.0 mmol) and $Ti(OEt)_4$ (1.9 mL, 9.0 mmol). The reaction was sealed with a septum under argon and stirred for 24 h. The reaction was then diluted with EtOAc, and the resulting solution was poured into brine. The suspension was filtered through Celite, and the filtrate was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was then crystallized from Et_2O/Hex, affording **1** as a pale yellow solid (611 mg, 52%): ^{1}H NMR

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.79 (t, J = 8.4 Hz, 2H), 3.19 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 6.81 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 7.34−7.23 (m, 4H), 7.49 (dt, J = 9.0 Hz, J = 1.5 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.99 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 35.4, 37.7, 55.3, 114.0, 126.9, 128.1, 129.6, 129.9, 130.1, 131.1, 131.2, 132.5, 134.7, 135.4, 144.6, 146.0, 158.2, 168.5; HRMS (FAB+) calcd for $C_{23}H_{24}NO_3S^+$ 394.1471 $^+$, measured 394.1483 [M + 1].

5-(4-Methoxyphenyl)-2,2-dimethylpentanal (4). Prepared according to the Heck protocol from ethyl 2,2,-dimethylpent-4-enoate[25] (1.7 g, 10.9 mmol), 4-iodoanisole (2.63 g, 11.0 mmol), and $Pd(OAc)_2$ (122 mg, 0.55 mmol, 5 mol %), in DMF (50 mL) and TEA (1.54 mL), followed by direct hydrogenation according to the alkene hydrogenation protocol to afford ethyl 2,2-dimethyl-5-phenylpentanoate as a colorless oil (1.39 g, 76% over two steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H), 1.54 (apparent d, J = 3.6 Hz, 4H), 2.52 (bt, J = 6.6 Hz, 2H), 3.78 (s, 3H), 4.09 (quart, J = 7.2 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H). The resulting ester (1.39 g, 5.29 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (302 mg, 7.93 mmol) in THF (32 + 22 mL) to afford pure product alcohol 2,2-dimethyl-5-phenylpentan-1-ol (1.17 g, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 6H), 1.30−1.25 (m, 3H), 1.58−1.50 (m, 2H), 2.53 (t, J = 7.8 Hz, 2H), 3.30 (s, 2H), 3.78 (s, 3H), 6.82 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H). The resulting alcohol (1.16 g, 5.23 mmol) was oxidized according to the PCC oxidation protocol employing PCC (2.54 g, 11.8 mmol) in DCM (25 mL) to afford aldehyde **4** (888 mg, 77%) as a colorless oil following chromatography on silica gel, eluting with 5% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 6H), 1.53−1.45 (bm, 4H), 2.53−2.51 (bm, 2H), 3.78 (s, 3H), 6.82 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 26.4, 35.5, 36.8, 45.8, 55.3, 113.9, 129.3, 134.1, 157.9, 206.4; HRMS (FAB+) calcd for $C_{14}H_{20}O_2$ 220.1463 [M], measured 220.1463 [M].

1-(3-(4-Methoxyphenyl)propyl)cyclohexanecarbaldehyde (6). Prepared according to the Heck protocol from methyl 1-allylcyclohexanecarboxylate (1.82 g, 10.0 mmol), 4-iodoanisole (2.58 g, 11.0 mmol), and $Pd(OAc)_2$ (67 mg, 0.30 mmol, 3 mol %), in DMF (50 mL), to afford (*E*)-methyl 1-(3-(4-methoxyphenyl)allyl)-cyclohexanecarboxylate as a pale yellow oil (1.62 g, 56%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34−1.18 (m, 6H), 1.62−1.54 (m, 2H), 2.12−2.06 (m, 2H), 2.36 (d, J = 7.5 Hz, 2H), 3.67 (s, 3H), 3.79 (s, 3H), 5.89−6.00 (m, 1H), 6.30 (d, J = 15.9 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H). The resulting alkene (1.62 g, 5.60 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (324 mg, 20% by wt) in EtOH (15 mL) to afford methyl 1-(3-(4-methoxyphenyl)propyl)-cyclohexanecarboxylate as a colorless oil (1.53 g, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33−1.12 (m, 6H), 1.52−1.48 (m, 6H), 2.05 (bd, J = 12.0 Hz, 2H), 2.49 (bs, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 6.81 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H). The resulting ester (1.53 g, 5.26 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (300 mg, 7.89 mmol) in THF (30 + 20 mL) followed by direct oxidation of the crude product alcohol according to PCC oxidation protocol to afford aldehyde **6** (980 mg, 72% over two steps) as a colorless oil following chromatography on silica gel, eluting with 8% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31−1.21 (m, 4H), 1.53−1.42 (m, 8H), 1.88−1.85 (m, 2H), 2.50 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 6.81 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 25.6, 25.9, 31.1, 35.5, 36.1, 49.8, 55.4, 113.9, 129.3, 134.1, 157.9, 207.3; HRMS (FAB+) calcd for $C_{17}H_{24}O_2$ 260.1776 [M], measured 260.1767 [M].

5-(4-Methoxyphenyl)-3,3-dimethylpentanal (8). Prepared according to the Heck protocol from methyl 3,3-dimethylpent-4-enoate (2.13 g, 15.0 mmol), 4-iodoanisole (3.86 g, 16.5 mmol), and $Pd(OAc)_2$ (100 mg, 0.45 mmol, 3 mol %), in DMF (75 mL) and TEA (2.3 mL) to afford (*E*)-methyl 5-(4-methylphenyl)-3,3-dimethylpent-4-enoate as a colorless oil (2.16 g, 58%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 6H), 2.38 (s, 2H), 3.62 (s, 3H), 3.78 (s, 3H), 6.15 (d, J = 16.2 Hz, 1H), 6.28 (d, J = 16.2 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H). The resulting alkene (2.16 g, 8.70 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (432 mg, 20% by wt) in EtOH (20 mL) to afford methyl 5-(4-methoxyphenyl)-3,3-dimethyl-pentanoate as a colorless oil (1.47 g, 67%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 6H), 1.58 (bt, J = 8.1 Hz, 2H), 2.28 (s, 2H), 2.54 (d, J = 8.1 Hz, 2H), 3.66 (s, 3H), 3.78 (s, 3H), 6.82 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.5 Hz, 2H). The resulting ester (1.47 g, 5.86 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (335 mg, 8.80 mmol) in THF (36 + 24 mL) followed by direct oxidation of the crude product alcohol according to the PCC oxidation protocol to afford aldehyde **8** (733 mg, 57% over two steps) as a colorless oil following chromatography on silica gel, eluting with 8% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 6H), 1.58−1.64 (m, 2H), 2.32 (s, 2H), 2.51−2.57 (m, 2H), 3.77 (s, 3H), 6.82 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 9.86 (t, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6, 29.7, 33.7, 45.2, 54.8, 55.3, 114.0, 129.2, 134.6, 157.9, 203.4; HRMS (FAB+) calcd for $C_{14}H_{21}O_2^+$ 221.1536 [M + 1], measured 221.1538 [M + 1].

5-(4-Methoxyphenyl)-3-methylpentanal (10). Triethyl phosphonoacetate (0.916 g, 4.08 mmol) was weighed into a flame-dried, two-neck round-bottom flask equipped with a magnetic bar. Dry THF (3 mL, 2 M) was added under an argon atmosphere. NaH (60% suspension in mineral oil, 120 mg) was washed properly and added to the reaction vessel. The reaction mixture was stirred at room temperature for 30 min. 4-(4-Methoxyphenyl)butan-2-one (0.73 g, 4.09 mmol) in a solution of THF (2 mL, 2 M) was added dropwise to the reaction mixture. The reaction was monitored by TLC. After 18 h, the mixture was concentrated in vacuo. The residue was then dissolved in diethyl ether (30 mL) and washed with saturated $NaHCO_3$ (10 mL). The organic layer was dried over $NaSO_4$. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel and eluted with EtOAc/Hex (5:95) to afford the corresponding ester (0.64 g, 63%) as a colorless oil. This ester was then subjected to the alkene hydrogenation protocol employing Pd/C 10% by wt (64 mg) dissolved in EtOH (7 mL) to afford ethyl 5-(4-methoxyphenyl)-3-methylpentanoate (0.511 g, 2.05 mmol, 50% yield over two steps), which was employed directly in the next step; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 2.48−2.67 (m, 2H), 2.34 (dd, J = 14.7, 6.2 Hz, 1H), 2.15 (dd, J = 14.8, 8.0 Hz, 1H), 2.00 (sext, J = 6.2 Hz, 1H), 1.59−1.65 (m, 1H), 1.47−1.52 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H). The ester (0.492 g, 1.97 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (0.112 g, 2.95 mmol) in THF (11 + 8 mL) to afford pure 5-(4-methoxyphenyl)-3-methylpentan-1-ol (0.376 g, 92%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.65−3.72 (m, 2H), 2.47−2.67 (m, 2H), 1.56−1.68 (m, 3H), 1.37−1.48 (m, 3H), 0.96 (d, J = 6.3 Hz, 3H). The intermediate alcohol (0.346 g, 1.66 mmol) was then oxidized according to the Swern oxidation protocol employing $(COCl)_2$ (0.99 mL of 2.0 M solution in DCM), DMSO (0.311 g, 3.98 mmol), and TEA (0.672 g, 6.65 mmol) in DCM (2 + 4 mL). The crude material was purified by silica gel column chromatography (8% Et_2O/Hex) to afford the pure aldehyde **10** (0.250 g, 73%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 2.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 2.54−2.63 (m, 2H), 2.44 (ddd, J = 16.0, 5.7, 2.0 Hz, 1H), 2.27 (ddd, J = 16.1, 7.9, 16.1 Hz, 1H), 2.08−2.13 (m, 1H), 1.51−1.66 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 158.2, 134.4; 129.6, 129.6, 114.2, 114.2, 55.7, 51.4, 39.3, 32.7, 28.1, 20.2; HRMS (FAB+) calcd for $C_{13}H_{18}O_2$ 207.1307 [M], measured 206.1324 [M].

Methyl 4-(3,3-Dimethyl-5-oxopentyl)phenylcarbamate (14). Prepared according to the Heck protocol from methyl 3,3-dimethylpent-4-enoate (1.30 g, 9.09 mmol), aryl iodide methyl 4-iodophenylcarbamate (2.77 g, 10.0 mmol), and $Pd(OAc)_2$ (102 mg, 0.45 mmol, 5 mol %), in DMF (45 mL) and TEA (2.5 mL) to afford methyl 5-(4-methoxycarbonylamino)phenyl)-3,3-dimethylpentenoate

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

as a colorless oil (1.38 g, 52%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 6H), 2.40 (s, 2H), 3.63 (s, 3H), 3.75 (s, 3H), 6.32−6.18 (m, 2H), 7.08 (bs, 1H), 7.33−7.27 (m, 4H). The resulting alkene (918 mg, 3.15 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (100 mg, 20% by wt) in EtOH (10 mL) to afford methyl 5-(4-methoxycarbonylamino)phenyl)-3,3-dimethylpentanoate as a colorless oil (877 mg, 95%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 6H), 1.61−1.55 (m, 2H), 2.28 (s, 2H), 2.58−2.52 (m, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 6.65 (bs, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H). A flame-dried flask was charged with $LiBH_4$ (196 mg, 9.0 mmol, 3 equiv), followed by the addition of THF (7 mL). The suspension was then cooled to 0 °C in an ice bath, and a solution of methyl 5-(4-methoxycarbonylamino)phenyl)-3,3-dimethylpentanoate in THF (3 mL) was added slowly. The reaction was then allowed to warm to room temperature and was stirred overnight. After complete reduction of the starting material, the mixture was diluted with water (50 mL) followed by the slow addition of 10% HCl (aq). The solution was then neutralized with saturated $NaHCO_3$, and the resulting solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude intermediate alcohol was employed directly in the next step. The alcohol was then subjected to the Swern oxidation protocol employing DMSO (0.51 mL, 7.20 mmol), oxalyl chloride 2 M in DCM (1.80 mL, 3.60 mmol), and triethylamine (1.70 mL, 12 mmol) in DCM (10 mL) to afford aldehyde **14** (603 mg, 76% over two steps) as a colorless oil following chromatography on silica gel, eluting with 30% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 6H), 1.64−1.58 (m, 2H), 2.34 (d, J = 3.0 Hz, 2H), 2.58−2.53 (m, 2H), 3.76 (s, 3H), 6.63 (bs, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 9.87 (t, J = 3.0 Hz, 1H); HRMS (FAB+) calcd for $C_{15}H_{21}NO_3$ 263.1521 [M], measured 263.1528 [M].

2,2-Dimethyl-5-phenylpentanal (16). Prepared according to the Heck protocol from ethyl 2,2,-dimethylpent-4-enoate[25] (1.56 g, 10.0 mmol), 4-iodobenzene (1.3 mL, 11.0 mmol), and $Pd(OAc)_2$ (67 mg, 0.30 mmol, 3 mol %) in DMF (50 mL) to afford (*E*)-ethyl 3,3-dimethyl-5-phenylpent-4-enoate as a pale yellow oil (1.85 g, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 6H), 1.25 (t, J = 7.2 Hz, 3H), 2.43 (dd, J = 7.5 Hz, J = 0.9 Hz, 2H), 4.13 (quart, J = 7.2 Hz, 2H), 6.20−6.09 (m, 1H), 6.40 (d, J = 15.9 Hz, 1H), 7.34−7.20 (m, 5H). The resulting alkene (1.85 g, 7.97 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (370 mg, 20% by wt) in EtOH (20 mL) to afford ethyl 3,3-dimethyl-5-phenylpentanoate as a colorless oil (1.70 g, 91%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H), 1.56 (bs, 4H), 2.59 (bs, 2H), 4.09 (quart, J = 7.2 Hz, 2H), 7.27−7.15 (m, 5H). The intermediate ester (1.70 g, 7.25 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (413 mg, 10.88 mmol) in THF (42 + 28 mL) followed by direct oxidation of the crude product alcohol according to the PCC oxidation protocol to afford aldehyde **16** (1.11 g, 81% over two steps) as a colorless oil following chromatography on silica gel, eluting with 5% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 6H), 1.55−1.51 (bm, 4H), 2.60 (t, J = 6.9 Hz, 2H), 7.30−7.14 (m, 5H), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 26.2, 36.5, 36.9, 45.9, 126.0, 128.5, 128.7, 142.1, 206.4; HRMS (FAB+) calcd for $C_{13}H_{18}O$ 190.1358 [M], measured 190.1371 [M].

5-(4-Methoxyphenyl)-2-methylpentanal (18). Prepared according to the Heck protocol from ethyl 2-methylpent-4-enoate (1.00 g, 7.03 mmol), 4-iodoanisole (1.81 g, 7.74 mmol), and $PdCl_2(PPh_3)_2$ (24 mg, 5 mol %) in DMF (28 mL) and TEA (0.78 g, 7.7 mmol) to afford (*E*)-ethyl-5-(4-methoxyphenyl)-2-methylpent-4-enoate as a pale yellow oil. The resulting alkene was hydrogenated according to the hydrogenation protocol employing Pd/C 10% by wt (99.0 mg) in EtOH (10.0 mL) to afford ethyl 5-(4-methoxyphenyl)-2-methylpentanoate (1.12 g, 4.5 mmol, 64% over two steps) which was employed directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.12 (q, J = 8.7 Hz, 2H), 3.79 (s, 3H), 2.55 (t, J = 7.4 Hz, 2H), 2.43 (t, J = 7.4 Hz, 1H), 1.54−1.73 (m, 3H), 1.43−1.49 (m, 1H), 1.24 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H). The crude ester (0.975 g, 3.90 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (0.222 g, 5.85 mmol) in THF (22 + 16 mL) to afford pure 5-(4-methoxyphenyl)-2-methylpentan-1-ol (0.722 g, 3.71 mmol, 95%) as a colorless oil following silica gel column chromatography, eluting with 20% EtOAc/Hex: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.33−3.48 (m, 2H), 2.49 (ddd, J = 8.8, 8.8, 2.6 Hz, 2H), 1.50−1.63 (m, 3H), 1.22−1.44 (m, 1H), 1.15 (bs, 1H), 1.03−1.10 (m, 1H), 0.85 (d, J = 6.7 Hz, 3H). The resulting alcohol (0.70 g, 3.36 mmol) was oxidized according to the Swern oxidation protocol employing $(COCl)_2$ (2.02 mL of 2.0 M solution in DCM), DMSO (0.630 g, 8.07 mmol), TEA (1.36 g, 13.4 mmol) in DCM (2 + 4 mL). The crude material was purified by silica gel column chromatography eluting with 5% EtOAc/Hex to afford the pure aldehyde **18** (0.506 g, 2.45 mmol, 73%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, J = 1.9 Hz, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 2.56 (t, J = 7.3 Hz, 2H), 2.33 (dsext, J = 6.9; 1.9 Hz, 1H), 1.57−1.76 (m, 3H), 1.34−1.43 (m, 1H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 158.2, 134.4; 129.7, 129.6, 114.2, 114.2, 55.6, 46.6, 35.3, 30.4, 29.3, 13.7; HRMS (FAB+) calcd for $C_{13}H_{18}O_2$ 206.1307 [M], measured 206.1321 [M].

5-(4-Methoxyphenyl)-3-phenylpentanal (20). Prepared according to the procedure for compound **10** from triethyl phosphonoacetate (0.821 g, 2.66 mmol), NaH from 60% mineral oil suspension (0.140 g), and 3-(4-methoxyphenyl)-1-phenylpropan-1-one (0.80 g, 3.33 mmol) in THF (4 + 4 mL). After purification using silica gel column chormatography (5% EtOAc/Hex) the corresponding ester was submitted to direct hydrogenation according to the hydrogenation protocol using Pd/C 10% by wt (80 mg) in EtOH (10 mL) to afford ethyl 5-(4-methoxyphenyl)-3-phenylpentanoate (0.52 g, 1.66 mmol, 50% over two steps) which was employed directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.34 (m, 2H), 7.19−7.28 (m, 3H), 7.01 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 3.12−3.23 (m, 1H), 2.60 (t, J = 6.1 Hz, 2H), 2.40 (t, J = 8.4 Hz, 2H), 1.86−1.97 (m, 2H), 1.12 (t, J = 6.9 Hz, 3H). The crude ester (0.75 g, 2.40 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (0.14 g, 3.61 mmol) in THF (14 + 10 mL) to afford pure 5-(4-methoxyphenyl)-3-phenylpentan-1-ol (0.616 g, 2.28 mmol, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 2H), 7.20 (dd, J = 5.5, 4.1 Hz, 3H), 7.01 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.43−3.56 (m, 2H), 2.72 (t, J = 7.9 Hz, 1H), 2.40 (t, J = 7.9 Hz, 2H), 1.86−1.99 (m, 4H), 1.56 (brs, 1H). The intermediate alcohol (0.53 g, 1.95 mmol) was oxidized according to the Swern oxidation protocol employing $(COCl)_2$ (1.17 mL of 2.0 M solution in DCM), DMSO (0.37 g, 4.68 mmol), TEA (0.79 g, 7.80 mmol) in DCM (2 + 4 mL). The crude product was purified by silica gel column chromatography 5% EtOAc/Hex to afford the pure aldehyde **20** (0.37 g, 1.36 mmol, 70%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (t, J = 2.1 Hz, 1H), 7.33 (t, J = 6.5 Hz, 2H), 7.21−7.23 (m, 3H) 7.01 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 3.19 (quintet, J = 7.4 Hz, 1H), 2.72 (ddd J = 7.4, 2.1, 1.3 Hz, 2H), 2.42 (ddd, J = 9.0, 9.0, 1.8 Hz, 2H), 1.90−1.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 158.2, 143.8; 134.1, 129.6, 129.6, 129.1, 129.1, 128.0, 128.0, 127.1, 114.2, 114.2, 55.6, 51.1, 39.9, 38.7, 32.0; HRMS (FAB+) calcd for $C_{18}H_{20}O_2$ 268.1463 [M], measured 268.1476 [M].

5-(2-Methoxyphenyl)-2-methylpentanal (22). Prepared according to the Heck protocol from ethyl 2-methylpent-4-enoate (1.00 g, 7.03 mmol), 2-iodoanisole (1.81 g, 7.74 mmol), and $PdCl_2(PPh_3)_2$ (24 mg, 5 mol %) in DMF (28 mL) and TEA (0.78 g, 7.7 mmol). The resulting alkene was submitted to the hydrogenation protocol using EtOH (10 mL) and Pd/C 10% by wt (100 mg) to afford ester ethyl 5-(2-methoxyphenyl)-2-methylpentanoate (0.88 g, 3.52 mmol, 50% over two steps) which was used directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (ddd, J = 9.6, 7.8, 1.8 Hz, 1H), 7.11 (dd, J = 7.4, 1.6 Hz, 1H), 6.82−6.89 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 2.45 (sext, J = 7.0 Hz, 1H), 1.65−1.73 (m, 1H), 1.56−1.61 (m, 2H), 1.40−1.50 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H). The crude ester

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

(0.87 g, 3.46 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (0.197 g, 5.19 mmol) in THF (17 + 14 mL) to afford pure 5-(2-methoxyphenyl)-2-methylpentan-1-ol (0.633 g, 3.04 mmol, 88%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.20 (m, 2H), 6.83−6.93 (m, 2H), 3.82 (s, 3H), 3.51 (dd, J = 10.4, 6.0 Hz, 1H), 3.42 (dd, J = 10.2, 6.6 Hz, 1H), 2.60 (ddd, J = 8.8, 6.9, 2.3 Hz, 2H), 1.41−1.70 (m, 4H), 1.30 (brs, 1H), 1.17−1.23 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H). The intermediate alcohol (0.77 g, 3.70 mmol) was oxidized according to the Swern oxidation protocol employing $(COCl)_2$ (2.21 mL of 2.0 M solution in DCM), DMSO (0.693 g, 8.90 mmol), TEA (1.50 g, 14.7 mmol) in DCM (3 + 6 mL). The crude product was purified by silica gel column chromatography eluting with 10% EtOAc/Hex to afford the pure aldehyde **22** (0.412 g, 2.0 mmol, 54%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, J = 2.0 Hz, 1H), 7.06−7.16 (m, 2H), 6.78−6.87 (m, 2H), 3.76 (s, 3H), 2.62 (t, J = 7.4 Hz, 2H), 2.33 (dsext, J = 7.0, 1.9 Hz, 1H), 1.59−1.73 (m, 3H), 1.36−1.42 (m, 1), 1.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 157.8, 130.7; 130.2, 127.6, 120.8, 110.7, 55.6, 46.6, 30.6, 30.6, 27.6, 13.7; HRMS (FAB+) calcd for $C_{13}H_{18}O_2$ 206.1307 [M], measured 206.1311 [M].

5-(3-Methoxyphenyl)-2-methylpentanal (24). Prepared according to the Heck protocol from ethyl 2-methylpent-4-enoate (1.00 g, 7.03 mmol), 2-iodoanisole (1.81 g, 7.74 mmol), and $PdCl_2(PPh_3)_2$ (24 mg, 5 mol %) in DMF (28 mL) and TEA (0.78 g, 7.7 mmol). The resulting alkene was submitted to the hydrogenation protocol using EtOH (10 mL) and Pd/C 10% by wt (100 mg) to afford ethyl 5-(3-methoxyphenyl)-2-methylpentanoate (0.65 g, 2.60 mmol, 37% over two steps) which was used directly in the next step; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (ddd, J = 7.4, 7.4, 2.0 Hz, 1H), 6.72−6.77 (m, 4H), 4.12 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.59 (t, J = 7.4 Hz, 2H), 2.43 (sext, J = 6.8 Hz, 1H), 1.56−1.72 (m, 3H), 1.42−1.50 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H). The crude ester (0.65 g, 2.60 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (0.150 g, 3.95 mmol) in THF (13 + 11 mL) to afford pure 5-(3-methoxyphenyl)-2-methylpentan-1-ol (0.285 g, 1.37 mmol, 53%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−7.22 (m, 1H), 6.72−6.79 (m, 3H), 3.80 (s, 3H), 3.42−3.49 (m, 2H), 2.59 (td, J = 7.9, 2.7 Hz, 2H), 1.60−1.68 (m, 2H), 1.57 (s, 1H), 1.42−1.46 (m, 1H), 1.18−1.25 (m, 2H), 0.92 (d, J = 6.7 Hz, 3H). The intermediate alcohol (0.510 g, 2.45 mmol) was oxidized according to the Swern oxidation protocol employing $(COCl)_2$ (1.50 mL of 2.0 M solution in DCM), DMSO (0.459 g, 5.87 mmol), TEA (0.99 g, 9.80 mmol) in DCM (2.5 + 1.5 mL). The crude product was purified by silica gel column chromatography eluting with 10% EtOAc/Hex to afford the pure aldehyde **24** (0.430 g, 2.08 mmol, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (dd, J = 1.9, 0.8 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.72−6.78 (m, 3H), 3.80 (s, 3H), 2.61 (t, J = 7.3 Hz, 2H), 2.35 (dsext, J = 7.0, 1.9 Hz, 1H), 1.63−1.71 (m, 3H), 1.48−1.41 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 159.7, 143.6; 129.3, 120.8, 114.2, 111.1, 55.0, 46.2, 35.9, 30.0, 28.6, 13.3; HRMS (FAB+) calcd for $C_{13}H_{18}O_2$ 206.1307 [M], measured 206.1311 [M].

5-Fluoro-2-(4-methoxyphenethyl)benzaldehyde (28). Prepared according to the Sonogashira conditions from 2-bromo-5-fluorobenzaldehyde (1.40 g, 6.88 mmol), 4-ethynylanisole (1.0 g, 7.57 mmol), $PdCl_2(PPh_3)_2$ (91 mg, 0.13 mmol, 2 mol %), and CuI (25 mg, 0.13 mmol, 2 mol %) in freshly distilled triethylamine (27 mL) to afford 5-fluoro-2-((4-methoxyphenyl)ethynyl)benzaldehyde as a white solid (1.63 g, 93%) following chromatography on silica gel, eluting with 10% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 6.90 (d, J = 8.7 Hz, 2H), 7.31−7.24 (m, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.63−7.58 (m, 2H), 10.58 (s, 1H). The intermediate alkyne (1.53 g, 6.00 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (300 mg, 20% by wt) in EtOH (15 mL), followed by direct oxidation of the crude product alcohol according to the manganese dioxide oxidation protocol to afford aldehyde **28** (1.21 g, 78% over two steps) as a white solid following chromatography on silica gel, eluting with 5% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.82 (t, J = 8.4 Hz, 2H), 3.24 (t, J = 8.0 Hz, 2H), 3.76 (s, 3H), 6.80 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.17−7.15 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 37.7, 55.3, 113.9, 116.9 (d, J = 21.6 Hz), 120.9 (d, J = 21.1 Hz), 129.6, 132.7, 133.1 (d, J = 6.9 Hz), 135.3 (d, J = 5.5 Hz), 140.2, 158.2, 161.5 (d, J = 245.8 Hz), 190.5; HRMS (FAB+) calcd for $C_{16}H_{15}FO_2$ 258.1056 [M], measured 258.1054 [M].

4-Fluoro-2-(4-methoxyphenethyl)benzaldehyde (30). Prepared according to the Sonogashira conditions from methyl 2-bromo-4-fluorobenzoate (1.6 mL, 6.88 mmol), 4-ethynylanisole (1.0 g, 7.57 mmol), $PdCl_2(PPh_3)_2$ (91 mg, 0.13 mmol, 2 mol %), and CuI (25 mg, 0.13 mmol, 2 mol %) in freshly distilled triethylamine (23 mL) to afford methyl 4-fluoro-2-((4-methoxyphenyl)ethynyl)benzoate as a yellow solid (1.81 g, 93%) following chromatography on silica gel, eluting with 20% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 3.94 (s, 3H), 6.88 (d, J = 9.0 Hz, 2H), 7.03 (dt, J = 7.8 Hz, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.98 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H). The intermediate alkyne (1.81 g, 6.37 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (362 mg, 20% by wt) in EtOH (22 mL) to afford methyl 4-fluoro-2-(4-methoxyphenylethyl)benzoate as a colorless oil (1.77 g, 96%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84 (dd, J = 8.4 Hz, J = 5.7 Hz, 2H), 3.22 (dd, J = 8.4 Hz, J = 5.7 Hz, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 6.83 (d, J = 8.4 Hz, 2H), 6.95−6.84 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.94 (dd, J = 8.7 Hz, J = 6.0 Hz, 1H). The resulting ester (1.75 g, 6.06 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (345 mg, 9.09 mmol) in THF (36 + 24 mL) followed by direct oxidation of the crude product alcohol according to the manganese dioxide oxidation protocol to afford aldehyde **30** (1.19 g, 76% over two steps) as a white solid following chromatography on silica gel, eluting with 15% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (t, J = 8.1 Hz, 2H), 3.27 (t, J = 8.1 Hz, 2H), 3.75 (s, 3H), 6.80 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 9.3 Hz, 1H), 7.09−6.99 (m, 3H), 7.81 (t, J = 7.8 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.9, 37.0, 55.2, 113.9 (d, J = 21.5 Hz), 113.9, 118.0 (d, J = 21.4 Hz), 129.5, 130.5, 132.8, 135.1 (d, J = 9.9 Hz), 147.9 (d, J = 8.8 Hz), 158.2, 165.7 (d, J = 254.9 Hz), 190.5; HRMS (FAB+) calcd for $C_{16}H_{15}FO_2$ 258.1056 [M], measured 258.1049 [M].

4,5-Difluoro-2-(4-methoxyphenethyl)benzaldehyde (32). Prepared according to the Sonogashira conditions from methyl 2-bromo-4,5-difluorobenzoate (1.72 mL, 6.88 mmol), 4-ethynylanisole (1.0 g, 7.57 mmol), $PdCl_2(PPh_3)_2$ (91 mg, 0.13 mmol, 2 mol %), and CuI (25 mg, 0.13 mmol, 2 mol %) in freshly distilled triethylamine (23 mL) to afford methyl 4,5-difluoro-2-((4-methoxyphenyl)ethynyl)-benzoate as a yellow solid (1.68 g, 81%) following chromatography on silica gel, eluting with 8% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 3.95 (s, 3H), 6.89 (d, J = 8.7 Hz, 2H), 7.40 (dd, J = 10.8 Hz, J = 7.8 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.81 (dd, J = 10.8 Hz, J = 8.4 Hz, 1H). The intermediate alkyne (1.68 g, 5.57 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (337 mg, 20% by wt) in EtOH (19 mL) to afford methyl 4,5-difluoro-2-(4-methoxyphenethyl)benzoate as a white solid (1.70 g, 99%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (dd, J = 8.4 Hz, J = 5.7 Hz, 2H), 3.20 (dd, J = 8.4 Hz, J = 5.7 Hz, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 6.83 (d, J = 8.4 Hz, 2H), 6.96 (dd, J = 11.1 Hz, J = 7.8 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.77 (dd, J = 11.1 Hz, J = 8.1 Hz, 1H). The resulting ester (1.70 g, 5.57 mmol) was reduced according to the $LiAlH_4$ reduction protocol employing $LiAlH_4$ (320 mg, 8.36 mmol) in THF (33 + 22 mL) followed by direct oxidation of the crude product alcohol according to the manganese dioxide oxidation protocol to afford aldehyde **32** (842 mg, 55% over two steps) as a white solid following recrystallization from Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84 (t, J = 8.4 Hz, 2H), 3.24 (t, J = 8.1 Hz, 2H), 3.78 (s, 3H), 6.80 (d, J = 8.7 Hz, 2H), 7.04−6.97 (m, 3H), 7.64 (dd, J = 10.5 Hz, J = 8.4 Hz, 1H), 10.03 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.9, 37.4, 55.4, 114.1, 119.6 (d, J = 17.3 Hz), 120.0 (d, J = 17.3 Hz), 129.6, 130.8, 132.2, 142.5, 149.8 (dd, J = 332.1 Hz, J = 13.1 Hz), 153.2 (dd, J = 340.5 Hz, J = 12.9 Hz), 158.4, 189.0; HRMS (FAB+) calcd for $C_{16}H_{14}F_2O_2$ 276.0962 [M], measured 276.0949 [M].

dx.doi.org/10.1021/jo300635m | J. Org. Chem. 2012, 77, 6689−6702

1-(4-Methoxyphenethyl)naphthalene-2-carbaldehyde (34). Prepared according to the Sonogashira conditions from 1-bromonaphthalene-2-carboxaldehyde (1.35 g, 5.73 mmol), 4-ethynylanisole (832 mg, 6.30 mmol), $PdCl_2(PPh_3)_2$ (97 mg, 0.14 mmol, 2.5 mol %), and CuI (27 mg, 0.14 mmol, 2.5 mol %) in freshly distilled triethylamine (23 mL) to afford 1-((4-methoxyphenyl)ethynyl)-naphthalene-2-carboxaldehyde as a yellow solid (1.18 g, 72%) following chromatography on silica gel, eluting with 10% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 6.97 (dd, J = 6.9 Hz, J = 2.1 Hz, 2H), 7.69−7.62 (m, 4H), 7.91−7.84 (m, 2H), 7.98 (d, J = 8.7 Hz, 1H), 8.61 (dd, J = 6.3 Hz, J = 3.6 Hz, 1H), 10.89 (s, 1H). The intermediate alkyne (1.18 g, 4.12 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (236 mg, 20% by wt) in EtOH (15 mL), followed by direct oxidation of the crude alcohol according to the manganese dioxide oxidation protocol to afford **34** (464 mg, 39%, across two steps) as a white solid following chromatography on silica gel, eluting with 15% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (t, J = 6.3 Hz, 2H), 3.82−3.77 (m, 2H, eclipsed by singlet at 3.79), 3.79 (s, 3H), 6.85 (dd, J = 6.6 Hz, J = 1.8 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.65−7.62 (m, 2H), 7.81 (d, J = 8.7 Hz, 1H), 7.93−7.88 (m, 2H), 8.32−8.28 (m, 1H), 10.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.0, 37.2, 55.4, 114.1, 124.6, 125.0, 127.1, 127.4, 128.6, 129.1, 129.5, 131.0, 131.9, 132.0, 136.4, 143.6, 158.3, 191.6; HRMS (FAB+) calcd for $C_{20}H_{19}O_2^+$ 291.1380 [M + 1], measured 291.1385 [M + 1].

2-(2-(Biphenyl-4-yl)ethyl)benzaldehyde (38.). To a flame-dried flask equipped with a magnetic stir bar was added 95% NaH (288 mg, 12.0 mmol) followed by DMF (40 mL). The resulting suspension was cooled to 0 °C and triphenyl-(2-carbomethoxybenzyl)phosphonium bromide[26] (5.88 g, 12 mmol) was added portionwise. Upon complete addition, the mixture was warmed to room temperature and stirred for 30 min. 4-Biphenyl carboxaldehyde (1.82 g, 10 mmol) was then added in one portion, and the mixture was stirred at room temperature for 12 h. Upon complete consumption of the aldehyde, the reaction mixture was poured into water (200 mL) and extracted with EtOAc. The combined organic layers were then washed twice with water and once with brine. The organic layer was dried over $MgSO_4$, and the resulting suspension was filtered. The filtrate was concentrated in vacuo, and the residue was then chromatographed on silica gel, eluting with 20% EtOAc/Hex, to afford (*E*)-methyl 2-(2-(biphenyl-4-yl)vinyl)benzoate as a white solid (3.14 g, 99%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (s, 3H), 7.04 (d, J = 16.4 Hz, 1H), 7.36−7.29 (m, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.63−7.58 (m, 6H), 7.73 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 16.4 Hz, 1H). The intermediate alkene (3.14 g, 9.99 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (640 mg, 20% by wt) in EtOH (25 mL), followed by direct reduction of the crude product ester according to the $LiAlH_4$ reduction protocol. The resulting crude alcohol was subjected to the manganese dioxide oxidation protocol to afford aldehyde **38** (1.74 g, 61% over three steps) as a white solid following chromatography on silica gel, eluting with 15% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.93 (dd, J = 8.4 Hz, J = 6.0 Hz, 2H), 3.34 (dd, J = 8.4 Hz, J = 5.7 Hz, 2H), 7.52−7.20 (m, 10H), 7.58 (d, J = 8.7 Hz, 2H), 7.82 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 10.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.1, 38.0, 126.9, 127.1, 127.2, 127.2, 128.8, 129.1, 131.4, 132.9, 133.9, 139.2, 140.5, 141.1, 144.3, 192.6; HRMS (FAB+) calcd for $C_{21}H_{18}O$ 286.1358 [M], measured 286.1367 [M].

2-(4-Methoxy-2-methylphenethyl)benzaldehyde (40). Prepared according to the hydrogenation protocol from alkyne 2-((4-methoxy-2-methylphenyl)ethynyl)benzaldehyde[27] (1.51 g, 6.00 mmol) and 10% by wt Pd/C (302 mg, 20% by wt) in EtOH (15 mL) followed by direct oxidation of the crude alcohol via the manganese dioxide oxidation protocol to afford aldehyde **40** (813 mg, 53% over two steps) following chromatography on silica gel, eluting with 8% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.84 (dd, J = 8.4 Hz, J = 6.0 Hz, 2H), 3.25 (dd, J = 8.4 Hz, J = 6.0 Hz, 2H), 3.77 (s, 3H), 6.70−6.65 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.38 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.49 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.82 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6, 33.9, 34.9, 55.3, 111.3, 115.9, 126.8, 130.3, 131.4, 131.6, 132.1, 133.9, 134.0, 137.4, 144.7, 158.1, 192.3; HRMS (FAB+) calcd for $C_{17}H_{18}O_2$ 254.1307 [M], measured 254.1317 [M].

2-(2-(6-Methoxynaphthalen-2-yl)ethyl)benzaldehyde (42). Prepared according to the Sonogashira conditions from 2-bromobenzaldehyde (1.17 mL, 10.0 mmol), 2-ethynyl-6-methoxynaphthalene (2 g, 11.0 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol, 2 mol %), and CuI (38 mg, 0.20 mmol, 2 mol %) in freshly distilled triethylamine (40 mL) to afford 2-((6-methoxynaphthalen-2-yl)-ethynyl)benzaldehyde as a white solid (1.90 g, 66%) following chromatography on silica gel, eluting with 20% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (s, 3H), 7.11 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 7.43 (dt, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.59−7.53 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.8 Hz, J = 2.4, 2H), 7.96 (d, J = 0.8 Hz, 1H), 8.00 (s, 1H), 10.70 (s, 1H). The intermediate alkyne (1.85 g, 6.74 mmol) was hydrogenated according to the hydrogenation protocol employing 10% by wt Pd/C (370 mg, 20% by wt) in EtOH (17 mL) followed by direct oxidation of the crude alcohol via the manganese dioxide oxidation protocol to afford aldehyde **42** (1.40 g, 75% over two steps) following chromatography on silica gel, eluting with 15% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.01 (t, J = 8.4 Hz, 2H), 3.37 (t, J = 8.4 Hz, 2H), 3.89, (s, 3H), 7.13−7.10 (m, 2H), 7.22 (d, J = 7.2 Hz, 1H), 7.39−7.31 (m, 2H), 7.48−7.43 (m, 1H), 7.52 (s, 1H), 7.68−7.63 (m, 2H), 7.82 (dd, J = 7.5 Hz, J = 0.9, 1H), 10.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.1, 38.3, 55.4, 105.7, 118.8, 126.6, 126.8, 126.9, 127.9, 129.0, 129.1, 131.4, 132.7, 133.2, 133.9, 136.5, 144.4, 157.3, 192.6; HRMS (FAB+) calcd for $C_{20}H_{18}O_2$ 290.1307 [M], measured 290.1312 [M].

3-(4-Methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (2). Purification by flash column chromatography on silica gel afforded **2** as a white solid, eluting with 15% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 3H), 3.05−3.03 (m, 2H), 3.73 (s, 3H), 4.14 (d, J = 17 Hz, 1H), 4.68 (d, J = 16.5 Hz, 1H), 5.37 (bs, 1H), 6.72 (d, J = 8.5 Hz, 2H), 6.99−6.97 (m, 1H), 7.05−7.03 (m, 1H), 7.13−7.10 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 32.2, 43.9, 54.1, 55.3, 113.8, 126.0, 126.5, 127.1, 127.2, 128.6, 128.8, 129.6, 131.8, 132.5, 132.7, 137.4, 143.3, 158.9; HRMS (FAB+) calcd for $C_{23}H_{24}NO_3S$ 394.1471 [M + 1], measured 394.1483 [M + 1].

2-(4-Methoxyphenyl)-5,5-dimethyl-1-tosylpiperidine (5). Purification by flash column chromatography on silica gel afforded **5** as a white solid, eluting with 25% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 6H), 1.28−1.22 (bm, 2H), 2.10−2.03 (bm, 2H), 2.39 (s, 3H), 2.84 (d, J = 13.5 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 3.77 (s, 3H), 5.16 (s, 1H), 6.77 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 24.2, 25.7, 28.7, 30.4, 32.6, 52.5, 55.0, 55.3, 113.8, 127.1, 128.2, 129.5, 130.8, 138.7, 142.8, 158.4; HRMS (FAB+) calcd for $C_{21}H_{28}NO_3S^+$ 374.1784 [M + 1], measured 374.1798 [M + 1].

3-(4-Methoxyphenyl)-2-tosyl-2-azaspiro[5.5]undecane (7). Purification by flash column chromatography on silica gel afforded **7** as a white solid, eluting with 15% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21−1.07 (m, 4H), 1.43−1.31 (m, 8H), 2.03−1.97 (m, 2H), 2.38 (s, 3H), 2.76 (d, J = 13.6 Hz, 1H), 3.69 (d, J = 13.6 Hz, 1H), 5.14 (t, J = 3.6 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 21.6, 25.0, 26.5, 30.9, 31.9, 32.7, 37.8, 50.0, 55.3, 113.8, 127.0, 128.2, 129.4, 130.9, 138.6, 142.7, 158.4; HRMS (FAB+) calcd for $C_{24}H_{32}NO_3S^+$ 414.2097 [M + 1], measured 414.2092 [M + 1].

2-(4-Methoxyphenyl)-4,4-dimethyl-1-tosylpiperidine (9). Purification by flash column chromatography on silica gel afforded **9** as a white solid, eluting with 15% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (s, 3H), 0.80 (s, 3H), 1.25 (t, J = 3.6 Hz, 2H), 1.49 (dd, J = 14.1 Hz, J = 5.7 Hz, 1H), 1.91 (dd, J = 14.1 Hz, J = 4.8 Hz, 1H), 2.41 (s, 3H), 3.46−3.37 (m, 1H), 3.69−3.63 (m, 1H), 3.77 (s, 3H), 4.93 (t, J = 4.8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 27.3, 28.9, 31.1, 37.3, 40.2, 42.7, 55.3, 113.6, 127.2,

127.5, 129.5, 132.9, 138.0, 142.9, 158.3; HRMS (FAB+) calcd for $C_{21}H_{28}NO_3S^+$ 374.1784 [M + 1], measured 374.1798 [M + 1].

***trans*-2-(4-Methoxyphenyl)-4-methyl-1-tosylpiperidine (11).** Purification by flash column chromatography on silica gel, eluting with 5% EtOAc/Hex, afforded **11** as a 93:7 *trans*/*cis* mixture. The major diastereomer was isolated by recrystallization of the mixture from diethyl ether with slow vapor diffusion of pentane. This material was used for characterization purposes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 5.27 (d, J = 5.0 Hz, 1H), 3.86 (d, J = 13.9 Hz, 1H), 3.79 (s, 3H), 2.97 (ddd, J = 13.5, 13.5, 2.6 Hz, 1H), 2.43 (s, 3H), 2.14 (d, J = 13.8 Hz, 1H), 1.61−1.48 (m, 1H), 1.37 (d, J = 13.1 Hz, 1H), 1.25 (ddd, J = 12.6, 12.6, 5.4 Hz, 1H), 0.90 (ddd, J = 16.8, 12.6, 4.5 Hz, 1H), 0.79 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 143.3, 139.2, 131.4, 130.0, 130.0, 128.4, 128.4, 127.4, 127.4, 114.3, 114.3, 55.7, 55.3, 42.8, 36.0, 33.3, 25.5, 22.6, 21.9; HRMS (FAB+) calcd for $C_{20}H_{26}NO_3S^+$ 360.1628 [M + 1], measured 360.1630 [M + 1]. An X-ray structure was also obtained; see the Supporting Information.

2-(4-Methoxyphenyl)-1-tosylpiperidine (13). Purification by flash column chromatography on silica gel afforded **13** as a colorless oil, eluting with 10% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48−1.29 (m, 5H), 2.16 (bd, J = 12.6 Hz, 1H), 2.44 (s, 3H), 2.99 (dt, J = 14.7 Hz, J = 3.3 Hz, 1H), 3.83−3.77 (m, 4H), 5.21 (s, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.31−7.24 (m, 4H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 21.7, 24.5, 27.4, 41.9, 55.0, 55.4, 114.1, 127.2, 128.4, 129.8, 131.0, 139.0, 143.0, 158.6; HRMS (FAB+) calcd for $C_{19}H_{24}NO_3S^+$ 346.1471 [M + 1], measured 346.1482 [M + 1].

Methyl 4-(4,4-Dimethyl-1-tosylpiperidin-2-yl)-phenylcarbamate (15). Purification by flash column chromatography on silica gel afforded **15** as a white solid, eluting with 40% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.57 (s, 3H), 0.80 (s, 3H), 1.28−1.23 (m, 2H), 1.52 (dd, J = 10.5 Hz, J = 4.2 Hz, 1H), 1.92 (dd, J = 10.5 Hz, J = 3.3 Hz, 1H), 2.42 (s, 3H), 3.42−3.35 (m, 1H), 3.68 (dt, J = 10.5 Hz, J = 3.3 Hz, 1H), 3.77 (s, 3H), 4.96 (t, J = 3.6 Hz, 1H), 6.56 (bs, 1H), 7.19 (d, J = 6.6 Hz, 2H), 7.29−7.25 (m, 4H), 7.65 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 27.2, 29.0, 31.3, 37.3, 40.2, 42.6, 52.4, 55.4, 118.6, 127.1, 127.3, 129.6, 136.2, 136.5, 138.0, 143.1, 154.1; HRMS (FAB+) calcd for $C_{22}H_{29}N_2O_4S^+$ 417.1843 [M + 1], measured 417.1849 [M + 1].

5,5-Dimethyl-2-phenyl-1-tosylpiperidine (17). Purification by flash column chromatography on silica gel afforded **17** as a golden oil, eluting with 5% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (s, 6H), 1.26−1.21 (m, 2H), 2.12−2.08 (m, 2H), 2.40 (s, 3H), 2.86 (d, J = 13.5 Hz, 1H), 3.41 (d, J = 13.5 Hz, 1H), 5.23 (bs, 1H), 7.27−7.14 (m, 7H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 24.2, 25.8, 28.8, 30.5, 32.6, 52.7, 55.5, 126.8, 127.1, 127.2, 128.6, 129.5, 138.7, 139.0, 142.9; HRMS (FAB+) calcd for $C_{20}H_{25}NO_2S$ 343.1606 [M], measured 343.1610 [M].

***cis*-2-(4-Methoxyphenyl)-5-methyl-1-tosylpiperidine (19).** Purification by flash column chromatography on silica gel, eluting with 10% EtOAc/Hex, afforded **19** as a 92:8 *cis*/*trans* mixture. The major diastereomer was isolated by recrystallization of the mixture from diethyl ether with slow vapor diffusion of pentane. This material was used for characterization purposes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.21 (d, J = 4.6 Hz, 1H), 3.80 (s, 3H), 3.79−3.75 (m, 1H), 2.53 (dd, J = 14.3, 11.7 Hz, 1H), 2.43 (s, 3H), 2.18 (ddd, J = 14.0, 5.2, 3.1 Hz, 1H), 1.64 (dddd, J = 14.0, 14.0, 5.4, 3.7 Hz, 1H), 1.50−1.37 (m, 2H), 1.07 (ddd, J = 13.5, 12.0, 3.3 Hz, 1H), 0.70 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 143.3, 139.2, 131.0, 130.0, 130.0, 128.5, 128.5, 127.4, 127.4, 114.3, 114.3, 55.6, 54.3, 48.5, 30.3, 28.1, 27.5, 21.9, 19.3; HRMS (FAB+) calcd for $C_{20}H_{26}NO_3S^+$ 360.1628 [M + 1], measured 360.1637 [M + 1]. An X-ray structure was also obtained; see the Supporting Information.

***trans*-2-(4-Methoxyphenyl)-4-phenyl-1-tosylpiperidine (21).** Purification by flash column chromatography on silica gel afforded **21** as a white solid, eluting with 10% EtOAc/Hex: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 9.0 Hz, 2H), 7.25 (t, J = 7.0 Hz, 2H), 7.18 (ddd, J = 7.3, 1.3, 1.3 Hz, 1H), 6.97 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.40 (d, J = 4.6 Hz, 1H), 4.00 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 3.12 (ddd, J = 14.7, 12.9, 3.1 Hz, 1H), 2.71 (ddd, J = 12.6, 3.4, 3.4 Hz, 1H), 2.46 (s, 3H), 2.35 (d, J = 13.9 Hz, 1H), 1.79 (ddd, J = 13.4, 13.4, 5.3 Hz, 1H), 1.57−1.55 (m, 1H), 1.45 (ddd, J = 17.3, 12.8, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 145.6, 143.6, 139.2, 130.8, 130.2, 130.2, 129.0, 129.0, 128.4, 128.4, 127.5, 127.5, 127.0, 127.0, 126.9, 114.6, 114.6, 55.7, 55.4, 42.1, 36.8, 34.6, 32.2, 21.9; HRMS (FAB+) calcd for $C_{25}H_{28}NO_3S^+$ 422.1784 [M + 1], measured 422.1790 [M + 1].

***cis*-2-(2-Methoxyphenyl)-5-methyl-1-tosylpiperidine (Major Diastereomer *cis*-23).** Purification by flash column chromatography on silica gel, eluting with 10% EtOAc/Hex afforded **23** as a 73:27 *trans*/*cis* mixture. The major diastereomer ***cis*-23** was isolated by recrystallization of the mixture from diethyl ether with slow vapor diffusion of pentane. This material was used for characterization purposes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 2H), 7.20−7.06 (m, 4H), 6.81 (d, J = 8.3 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 5.50 (d, J = 5.8 Hz, 1H), 3.95 (dd, J = 13.3, 4.5 Hz, 1H), 3.79 (s, 3H), 2.96 (dd, J = 13.2, 11.7 Hz, 1H), 2.38 (s, 3H), 2.17−2.12 (m, 1H), 1.75−1.64 (m, 2H), 1.55−1-.42 (m, 2H), 0.95−0.91 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 143.0, 138.7, 129.9, 129.7, 129.7, 128.2, 128.1, 127.3, 127.3, 120.3, 110.9, 55.5, 51.7, 50.3, 30.8, 29.7, 28.1, 21.8, 19.5; HRMS (FAB+) calcd for $C_{20}H_{26}NO_3S^+$ 360.1628 [M + 1], measured 360.1647 [M + 1].

***trans*-2-(2-Methoxyphenyl)-5-methyl-1-tosylpiperidine (Minor Diastereomer *trans*-23).** Purification by flash column chromatography on silica gel afforded ***trans*-23** as a white solid, eluting with 10% EtOAc/Hex. The minor diastereomer was isolated after several silica gel chromatography columns. This material was used for characterization purposes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 1H), 7.12 (m, 3H), 6.80 (ddd, J = 7.7, 7.7, 1.0 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.75 (dd, J = 7.9, 4.6 Hz, 1H), 3.88 (dd, J = 12.5, 4.2 Hz, 1H), 3.70 (s, 3H), 2.84 (dd, J = 12.7, 7.7 Hz, 1H), 2.37 (s, 3H), 1.98−1.95 (m, 2H), 1.85−1.83 (m, 1H), 1.73−1.68 (m, 1H), 1.10−1.07 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 142.4, 136.4, 129.3, 129.1, 128.9, 128.9, 128.1, 127.5, 127.5, 119.9, 110.0, 55.0, 54.6, 52.1, 29.5, 29.5, 29.5, 21.5, 18.9; HRMS (FAB+) calcd for $C_{20}H_{26}NO_3S^+$ 360.1628 [M + 1], measured 360.1637 [M + 1].

***(Z)*-1-Methoxy-8-methyl-6,7-dihydro-5*H*-benzo[7]annulene (25).** Purification by flash column chromatography on silica gel afforded **25**, eluting with 5% EtOAc/Hex: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.3 Hz, 1H), 6.69−6.63 (m, 2H), 6.21 (s, 1H), 3.79 (s, 3H), 2.78−2.75 (m, 2H), 2.30 (t, J = 6.8 Hz, 2H), 1.98−1.94 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 142.7, 137.7; 131.5, 129.6, 125.4, 114.6, 110.7, 55.2, 36.6, 35.8, 27.1, 27.0; HRMS (FAB+) calcd for $C_{13}H_{17}O^+$ 189.1274 [M + 1], measured 189.1290 [M + 1].

7-Fluoro-3-(4-methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (29). Purification by flash column chromatography on silica gel afforded **29** as a white solid, eluting with 15% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.99 (bd, J = 4.0 Hz, 2H), 3.71 (s, 3H), 4.08 (d, J = 16.8 Hz, 1H), 4.66 (d, J = 16.8 Hz, 1H), 5.35 (t, J = 4.4 Hz, 1H), 6.68 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.72 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 6.82 (dt, J = 8.8 Hz, J = 2.8 Hz, 1H), 7.00 (dd, J = 8.4 Hz, J = 6.0 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 31.2, 43.7, 54.0, 55.3, 122.6 (d, J = 21.7 Hz), 113.8, 114.3 (d, J = 21.3 Hz), 127.1, 128.3, 128.5, 129.6, 130.2 (d, J = 7.8 Hz), 131.3, 134.2 (d, J = 7.0 Hz), 137.3, 143.4, 159.0, 161.2 (d, J = 243.7 Hz); HRMS (FAB+) calcd for $C_{23}H_{23}FNO_3S^+$ 412.1377 [M + 1], measured 412.1375 [M + 1].

6-Fluoro-3-(4-methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (31). Purification by flash column chromatography on silica gel afforded **31** as a white solid, eluting with 20% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.00 (s, 2H), 3.71 (s, 3H), 4.09 (d, J = 16.5 Hz, 1H), 4.66 (d, J = 16.5 Hz, 1H), 5.35 (t, J = 3.9 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.84−6.77 (m, 2H), 6.96−6.92

(m, 1H), 7.10 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 32.1, 43.3, 53.6, 55.2, 113.6 (d, J = 21.1 Hz), 113.8, 115.2 (d, J = 21.7 Hz), 127.1, 127.4 (d, J = 8.2 Hz), 128.4, 129.4, 129.6, 131.3, 135.0 (d, J = 7.7 Hz), 137.3, 143.3, 159.0, 161.6 (d, J = 243.9 Hz); HRMS (FAB+) calcd for $C_{23}H_{23}FNO_3S^+$ 412.1377 [M + 1], measured 412.1375 [M + 1].

6,7-Fluoro-3-(4-methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (33). Purification by flash column chromatography on silica gel afforded **33** as a white solid, eluting with 10% EtOAc/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 2.97 (bd, J = 3.6 Hz, 2H), 3.74 (s, 3H), 4.00 (d, J = 16.8 Hz, 1H), 4.62 (d, J = 16.8 Hz, 1H), 5.35 (t, J = 4.2 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.90−6.78 (m, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 31.1, 43.0, 53.5, 55.3, 114.0, 114.7 (d, J = 17.8 Hz), 117.3 (d, J = 17.0 Hz), 127.2, 128.4, 128.8, 129.3, 129.7, 130.9, 137.3, 143.6, 148.8 (dd, J = 244.7 Hz, J = 11.5 Hz), 149.4 (dd, J = 243.0, Hz, J = 9.4 Hz), 159.1; HRMS (FAB+) calcd for $C_{23}H_{21}F_2NO_3S$ 429.1210 [M], measured 429.1214 [M].

3-(4-Methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydrobenzo[f]-isoquinoline (35). Purification by flash column chromatography on silica gel afforded **35** as a white solid, eluting with 30% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 3.20 (dd, J = 17.1 Hz, J = 6.3 Hz, 1H), 3.57 (d, J = 17.1 Hz, 1H), 3.67 (s, 3H), 4.18 (d, J = 17.4 Hz, 1H), 4.81 (d, J = 17.7 Hz, 1H), 5.61 (d, J = 6.3 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 7.11−7.03 (m, 5H), 7.53−7.44 (m, 2H), 7.67−7.62 (m, 3H), 7.87−7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 27.1, 43.6, 53.3, 55.3, 113.8, 122.5, 124.2, 125.7, 126.6, 126.9, 127.1, 127.6, 128.8, 129.6, 131.0, 131.8, 132.7, 137.7, 143.3, 159.0; HRMS (FAB+) calcd for $C_{27}H_{26}NO_3S^+$ 444.1628 [M + 1], measured 444.1616 [M + 1].

3-(Biphenyl-4-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (39). Purification by flash column chromatography on silica gel afforded **39** as a white solid, eluting with 20% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.10 (d, J = 4.2 Hz, 2H), 4.25 (d, J = 16.5 Hz, 1H), 4.72 (d, J = 16.5 Hz, 1H), 5.43 (t, J = 4.5 Hz, 1H), 7.03−7.00 (m, 1H), 7.08−7.05 (m, 1H), 7.18−7.13 (m, 4H), 7.28−7.25 (m, 2H), 7.33 (d, J = 7.2 Hz, 1H), 7.44−7.38 (m, 4H), 7.51 (d, J = 6.9 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 32.6, 44.3, 54.7, 126.0, 126.6, 127.1, 127.2, 127.3, 127.4, 127.8, 128.8, 128.9, 129.7, 132.6, 132.7, 137.4, 139.0, 140.4, 140.8, 143.3; HRMS (FAB+) calcd for $C_{28}H_{26}NO_2S^+$ 440.1679 [M + 1], measured 440.1680 [M + 1]. The X-ray structure was also obtained; see the Supporting Information.

3-(4-Methoxy-2-methylphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (41). Purification by flash column chromatography on silica gel afforded **41** as a white solid, eluting with 20% EtOAc/Hex. The product was isolated as a 3:1 mixture of rotomers. Elevated temperature ^{1}H NMR failed to result in coalescence of the signals. For the purposes of spectral characterization the major and minor rotomers designated as a and b, respectively: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 0.91H^b), 2.30 (s, 3H^a), 2.41 (s, 0.97H^b), 2.50 (s, 3H^a), 2.85−2.77 (m, 1H^a + 0.44H^b), 3.07−3.01 (m, 1H^a + 0.67H^b), 3.17 (dd, J = 11.1 Hz, J = 4.8 Hz, 0.32H^b), 3.53 (s, 0.96H^b), 3.72 (s, 3H^a), 4.13 (d, J = 12.0 Hz, 0.32H^b), 4.21 (d, J = 12.3 Hz, 1H^a), 4.63 (d, J = 12.6 Hz, 1H^a), 4.76 (d, J = 11.7 Hz, 0.30H^b), 5.43−5.41 (m, 1H^a + 0.31H^b), 6.04 (d, J = 1.5 Hz, 0.29H^b), 6.44 (dd, J = 6.3 Hz, J = 2.1 Hz, 0.98H^b), 6.51 (d, J = 1.8 Hz, 0.35H^b), 6.70 (d, J = 2.1 Hz, 1H^a), 6.77 (d, J = 6.6 Hz, 1H^a), 6.93−6.91 (m, 1H + 0.39H^b), 7.19−7.00 (m, 6H^a + 1.5H^b), 7.29 (d, J = 6.0 Hz, 0.69H^b), 7.53 (d, J = 6.0 Hz, 2H^a), 7.78 (d, J = 6.0 Hz, 0.63H^b); ^{13}C NMR ($CDCl_3$, 75 MHz) δ18.6, 20.0, 21.5, 32.4, 41.7, 45.0, 50.4, 52.4, 52.7, 55.2, 105.1, 110.8, 116.4, 116.9, 125.5, 125.9, 126.5, 126.6, 126.8, 127.3, 127.4, 127.7, 127.8, 128.1, 128.3, 128.7, 129.2, 129.9, 131.2, 131.6, 133.2, 133.4, 134.8, 136.0, 136.8, 137.7, 138.0, 140.2, 143.1, 143.5, 158.8, 159.5; HRMS (FAB+) calcd for $C_{24}H_{26}NO_3S^+$ 408.1628 [M + 1], measured 408.1652 [M + 1].

3-(6-Methoxynaphthalen-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (43). Purification by flash column chromatography on silica gel afforded **43** as a white solid, eluting with 20% Et_2O/Hex: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.19−3.06 (m, 2H), 3.88 (s, 3H), 4.19 (d, J = 16.5 Hz, 1H), 4.73 (d, J = 16.8 Hz, 1H), 5.53−5.50 (m, 1H), 6.99−6.96 (m, 1H), 7.15−7.05 (m, 7H), 7.36 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H), 7.44, (s, 1H), 7.47 (d, J = 16.2 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 32.1, 44.2, 54.8, 55.4, 105.6, 118.9, 126.0, 126.1, 126.5, 127.2, 128.5, 128.8, 129.6, 132.5, 132.7, 133.9, 134.9, 137.4, 143.3, 157.9; HRMS (FAB+) calcd for $C_{27}H_{25}NO_3S$ 443.1555 [M], measured 443.1557 [M].

3-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (44). Napthalene (0.274 g, 2.14 mmol) was dissolved in dry DME (1.5 M), and sodium (0.039 g, 1.69 mmol) was added in portions. The mixture was stirred at room temperature for 1 h. It was then added dropwise to a solution of the tosylamine **2** (0.060 g, 0.152 mmol) in DME (0.09 M) at −78 °C until a green color persisted. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (80% EtOAc/MeOH) to afford **44** (0.039 g, 0.135 mmol, 89%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.16−7.10 (m, 4H), 6.91 (d, J = 8.7 Hz, 2H), 3.97 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 2.96 (d, J = 7.1 Hz, 2H), 1.99 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 136.3, 135.0, 134.9, 129.2, 127.8, 127.8, 126.4, 126.3, 114.1, 114.1, 58.0, 55.4, 49.3, 37.7, 29.8; HRMS (FAB+) calcd for $C_{16}H_{17}NO$ 239.1310 [M], measured 239.1315 [M].

***cis*-2-(4-Methoxyphenyl)-5-methylpiperidine (45).** Napthalene (0.464 g, 3.62 mmol) was dissolved in dry DME (1.5 M), and sodium (0.065 g, 2.83 mmol) was added in portions. The mixture was stirred at room temperature for 1 h. It was added dropwise to a solution of the tosylamine **19** (0.093 g, 0.260 mmol) in DME (0.09 M) at −78 °C until a green color persisted. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic layers were extracted with HCl 10%. The resulting aqueous layers were combined and washed with ethyl acetate. The aqueous layer was then neutralized with NaOH 1 N and subsequently extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **45** (0.046 g, 0.226 mmol, 87%) as a pale yellow oil that was pure by NMR analysis (mixture of diastereomers 90:10 *cis*/*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.58 (d, J = 9.2 Hz, 1H), 2.98 (dd, J = 11.7, 3.3 Hz, 1H), 2.84 (d, J = 11.7 Hz, 1H), 1.79−1.73 (m, 4H), 1.58 (d, J = 10.1 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 137.9, 128.1, 128.1, 114.1, 114.1, 61.3, 55.6, 52.7, 31.1, 29.8, 28.1, 17.6; HRMS (FAB+) calcd for $C_{13}H_{20}NO^+$ 206.1539 [M + 1], measured 206.1544 [M + 1].

Chiral Substrate (*S*)-5-(4-Methoxyphenyl)-2-methylpentanal (S5). To a suspension of (4*S*)-4-benzyl-oxazolidin-2-one (**S1**) (0.131 g, 0.739 mmol), DMAP (0.012 g, 0.098 mmol), and 5-(4-methoxyphenyl)pentanoic acid[23a] (0.20 g, 0.96 mmol) in DCM (0.75 M in oxazolidinone) at 0 °C under an argon atmosphere was added DCC (0.200 g, 1.00 mmol) in one portion. The reaction was warmed to room temperature after 10 min, and stirring was continued until no starting material was detected by TLC. The suspension was filtered through Celite, and the precipitate was washed with DCM. The filtrate was washed with sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated at reduced pressure. The resulting residue was purified by silica gel chromatography, eluting with 20% EtOAc/Hex to afford (*S*)-4-benzyl-3-(5-(4-methoxyphenyl)pentanoyl)oxazolidin-2-one (**S2**) (0.243 g, 0.662 mmol, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.33 (m, 3H), 7.23 (d, J = 7.1 Hz, 2H), 7.14 (d, 8.7 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 4.68 (oct, J = 8.3 Hz, 1H), 4.19−4.18 (m, 2H), 3.81 (s, 3H), 3.31 (dd, J = 13.4, 3.1 Hz, 1H), 3.01−2.98 (m, 2H), 2.79 (dd, J = 13.4, 9.6 Hz, 1H), 2.65 (t, J = 7.2 Hz, 2H), 1.76−1.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 157.8, 153.5, 135.4, 134.2, 129.5, 129.5, 129.3, 129.3, 129.0, 129.0, 127.3, 114.8, 113.8, 113.8 66.2, 55.3, 55.1, 37.9, 35.4, 34.7, 31.1, 23.9. To a stirred solution of *N*,*N*-diisopropylamine (0.275, 2.72 mmol) in anhydrous THF (0.4 M) at −78 °C was added a 2.5 M solution of n-BuLi in hexanes (1.8 mL). After stirring for 15 min at −78 °C, **S2**

dx.doi.org/10.1021/jo300635m | *J. Org. Chem.* 2012, 77, 6689−6702

(0.833 g, 2.26 mmol) in THF (0.8 M) was added dropwise. The mixture was stirred for 30 min after which methyl iodide (1.29 g, 0.09 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction was then quenched with 0.1 M aqueous HCl solution and extracted four times with Et_2O. The extract was washed once with brine, dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude product, which was purified by silica gel chromatography, eluting with 15% EtOAc/Hex to afford (*S*)-4-benzyl-3-((*S*)-5-(4-methoxyphenyl)-2-methylpentanoyl)oxazolidin-2-one (**S3**) (0.632 g, 1.66 mmol, 73%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 3H), 7.20 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.68−4.59 (m, 1H), 4.15−4.13 (m, 2H), 3.77 (s, 3H), 3.74 (q, J = 6.7 Hz, 1H), 3.24 (dd, J = 13.4, 3.1 Hz, 1H), 2.76 (dd, J = 13.4, 9.6 Hz, 1H), 2.65 (dd, J = 12.9, 7.1 Hz, 2H), 1.83−1.76 (m, 1H), 1.66−1.56 (m, 2H), 1.47−1.45 (m, 1H), 1.21 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 158.2, 153.4, 135.7, 134.7, 129.8, 129.8, 129.7, 129.3, 129.3, 127.7, 114.1, 114.1, 66.4, 55.7, 55.6, 38.3, 38.0, 35.3, 33.4, 29.6, 17.9; HRMS (FAB+) calcd for $C_{23}H_{28}NO_4^+$ 382.2013 [M + 1], measured 382.2029 [M + 1]. (*S*)-4-Benzyl-3-((*S*)-5-(4-methoxyphenyl)-2-methylpentanoyl)oxazolidin-2-one (**S3**) (0.60 g, 1.57 mmol) was dissolved in dry THF (0.3 M in ester) under an argon atmosphere and cooled to 0 °C. EtOH was added (101 uL), followed by $LiBH_4$ (0.041 g, 1.88 mmol). The mixture was then stirred overnight. Following the disappearance of the starting material as detected by TLC, EtOAc was added followed by the careful addition of saturated NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield (*S*)-5-(4-methoxyphenyl)-2-methylpentan-1-ol (**S4**) (0.274 g, 1.31 mmol) as a colorless oil following purification by silica gel column chromatography, eluting with 20% EtOAc/Hex: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H), 3.45 (s, 2H), 2.55 (ddd, J = 8.8, 8.8, 2.6 Hz, 2H), 1.63−1.50 (m, 3H), 1.44−1.32 (m, 1H), 1.22 (bs, 1H), 1.15−1.03 (m, 1H), 0.91 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 135.2, 129.6, 129.6, 114.1, 114.1, 68.6, 55.6, 36.1, 35.7, 33.2, 29.5, 17.0. Oxidation was carried out according to the Swern oxidation protocol from (*S*)-5-(4-methoxyphenyl)-2-methylpentan-1-ol (**S4**) (0.439 g, 2.11 mmol) and $(COCl)_2$ (1.26 mL of 2.0 M solution in DCM), DMSO (0.395 g, 5.06 mmol), TEA (0.853 g, 8.44 mmol) in DCM (2 + 4 mL). The crude reaction residue was purified by silica gel column chromatography 5% EtOAc/Hex to afford the pure (*S*)-5-(4-methoxyphenyl)-2-methylpentanal (**S5**) (0.305 g, 1.49 mmol, 70%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, J = 1.9 Hz, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 2.56 (t, J = 7.3 Hz, 2H), 2.33 (dsext, J = 6.9; 1.9 Hz, 1H), 1.76−1.57 (m, 3H), 1.43−1.34 (m, 1H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 158.2, 134.4; 129.7, 129.6, 114.2, 114.2, 55.6, 46.6, 35.3, 30.4, 29.3, 13.7; HRMS (FAB+) calcd for $C_{13}H_{19}O_2^+$ 207.1380 [M + 1], measured 207.1390 [M + 1].

(*S*)-2-(Methoxymethyl)-*N*-((*S*)-5-(4-methoxyphenyl)-2-methylpentylidene)pyrrolidin-1-amine (S6). The enantiomeric excess of aldehyde **S5** was determined by conversion of the aldehyde to the 1-amino-2-(methoxymethyl)pyrrolidine (SAMP) imine. SAMP (0.054 g, 0.415 mmol) was added to **S5** (0.103 g, 0.500 mmol) at 0 °C in the absence of solvent. After 1 h, the reaction mixture was dissolved in DCM, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was analyzed by ^{1}H NMR, which indicated a diastereomeric ratio of >99:1. The residue was purified by silica gel column chromatography eluting with 20% EtOAc/Hex to afford (*S*)-2-(methoxymethyl)-*N*-((*S*)-5-(4-methoxyphenyl)-2-methylpentylidene)pyrrolidin-1-amine (**S6**) (0.137 g, 0.430 mmol, 86%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 7.1 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 6.5 Hz, 1H), 3.77 (s, 3H), 3.57 (ddd, J = 8.9, 3.5, 1.7 Hz, 1H), 3.44−3.32 (m, 6H), 2.69 (quintet, J = 8.7 Hz, 1H), 2.54 (t, J = 7.0 Hz, 2H), 2.33 (septet, J = 6.8 Hz, 1H), 1.93−1.88 (m, 4H), 1.61 (quintet, J = 7.6 Hz, 2H), 1.45−1.37 (m, 2H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 144.2, 144.2, 134.8, 129.3, 129.3, 113.7, 113.7, 74.8, 63.6, 59.2, 55.2, 50.5, 37.0, 35.1, 35.1, 29.3, 22.1, 19.1; HRMS (FAB+) calcd for $C_{19}H_{31}N_2O_2^+$ 319.2386 [M + 1], measured 319.2379 [M + 1].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of HT-amination substrates and products, X-ray data for compounds **11**, **19**, and **39** (CIF), and discussion of the reactivity of chiral substrates. This material is available free of charge via the Internet at http://pubs.acs.org

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■ ACKNOWLEDGMENTS

This work was supported by the National Institute of General Medical Sciences (GM60326). We also thank the Parkin research group for X-ray crystal analysis. The National Science Foundation (CHE-0619638) is thanked for acquisition of an X-ray diffractometer.

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