JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

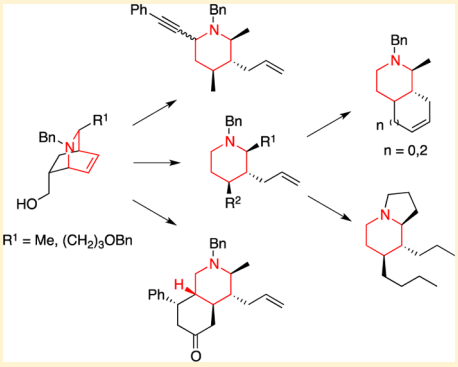
Grob Fragmentation of 2-Azabicyclo[2.2.2]oct-7-ene: Tool for the Stereoselective Synthesis of Polysubstituted Piperidines

Gérald Lemonnier and André B. Charette*

Centre in Green Chemistry and Catalysis, Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal QC H3C 3J7, Canada

Supporting Information

ABSTRACT: The Grob fragmentation of azabicyclo[2.2.2]octene leads to a dihydropyridinium intermediate. This highly reactive species reacts with a variety of organocuprates and other soft nucleophiles in a regioselective manner, allowing for the rapid and stereoselective synthesis of 2,3,4-trisubstituted 1,2,3,4-tetrahydropyridines. The resulting products were either reduced in situ to the corresponding piperidine or used to achieve the stereoselective construction of various nitrogen heterocycles.



Piperidine heterocycles are found in a wide variety of biologically active natural products[1] and are often key pharmacophores in drug design.[2] Consequently, significant efforts have been devoted to their efficient synthesis.[3] However, the emergence of new stereoselective methods for the preparation of polysubstituted piperidines is still required because of the numerous possible substitution patterns inherent to the complexity of such a ring.[4]

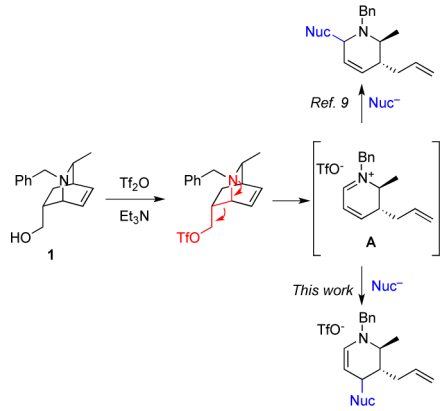
In particular, only a few examples of stereoselective synthesis of 2,3,4-trisubstituted piperidines have been published. The piperidine ring can be formed either through aza-Diels–Alder reactions,[5] intramolecular reductive aminations,[6] intramolecular allene hydroaminations,[7] or intramolecular aza-Michael additions.[8] All of these methods are multistep syntheses and often lack generality.

Our group has developed several stereoselective methodologies to access various substituted piperidines and related heterocycles.[9] Recently, we disclosed the efficient formation of the dihydropyridinium intermediate **A** from the aza-bicyclo[2.2.2]octene **1**[10] via a Grob fragmentation induced by triflic anhydride (Scheme 1).[9b] A subsequent Grignard addition to **A** leads to the 2,3,6-trisubstituted tetrahydropyridine.

Herein, we report the 1,4-addition of soft nucleophiles to the dihydropyridinium **A**, thus providing access to 2,3,4-trisubstituted piperidines.

Initially, we investigated the addition of organocuprates to the dihydropyridinium intermediate **A**. In this particular system, 1,4-addition of a nucleophile leads to a 1,2,3,4-tetrahydropyridine. Although the addition proceeded smoothly under our reaction conditions, several side reactions occurring during workup and purification procedures were observed, mainly due to the propensity of the enamine product to dimerize. To avoid these undesired reactions, the tetrahydropyridine was reduced in situ into the corresponding piperidine.

Scheme 1. Tf_2O-Induced Grob Fragmentation

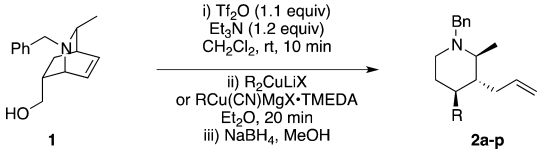


After extensive optimization, we found that the optimal cuprate was dependent upon the nature of the desired group at the 4-position using either Gillman's reagent (R_2CuX) (method A) or a mixed cyanocuprate ($RCu(CN)X$) in the presence of TMEDA as ligand (method B).[11] As depicted in Table 1, piperidines **2a–p** were obtained from the aza-bicyclo[2.2.2]-octene **1** through a one-pot fragmentation/cuprate addition/reduction process with good to excellent yields and excellent diastereoselectivity. Alkyl cuprates (entries 1–12), as well as aryl cuprates (entries 13–16), were successfully added. Interestingly, sterically demanding cuprates, such as *tert*-butyl

Received: April 25, 2012

   dx.doi.org/10.1021/jo300690h | J. Org. Chem. XXXX, XXX, XXX–XXX

Table 1. Cuprate Addition and Subsequent Tetrahydropyridine Reduction



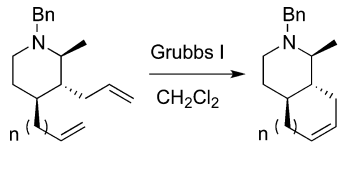
entry	R	X	product	method[a]	yield[b] (%)
1	Me	Li	**2a**	A	84
2	*i*-Pr	MgCl	**2b**	B	87
3	*n*-Bu	MgCl	**2c**	B	83
4	*i*-Bu	MgCl	**2d**	B	78
5	*t*-Bu	MgCl	**2e**	B	75
6	$PhCH_2CH_2$	MgCl	**2f**	B	77
7	3-butenyl	MgCl	**2g**	B	84
8	Bn	MgCl	**2h**	B	64
9	$TMSCH_2$	MgCl	**2i**	A	89
10	vinyl	MgBr	**2j**	A	51
11	Cp	MgCl	**2k**	B	42
12	Cy	MgCl	**2l**	B	69
13	Ph	MgBr	**2m**	B	84
14	*p*-Cl-Ph	MgBr	**2n**	B	93
15	*m*-$(TMS)_2$N-Ph	MgCl	**2o**	B	64
16	mesityl	MgBr	**2p**	B	86

[a]Preparation of the organocuprate reagent. Method A: from RMgX or RLi (4.8 equiv) and CuI (2.4 equiv), addition at rt. Method B: from RMgX (2.2 equiv), CuCN (2.5 equiv), and TMEDA (2.5 equiv), addition at −78 °C. See the Supporting Information for details. [b]All piperidines were isolated as single diastereoisomers.

cuprate (entry 5) or mesityl cuprate (entry 16), were also found to be suitable nucleophiles in this process.

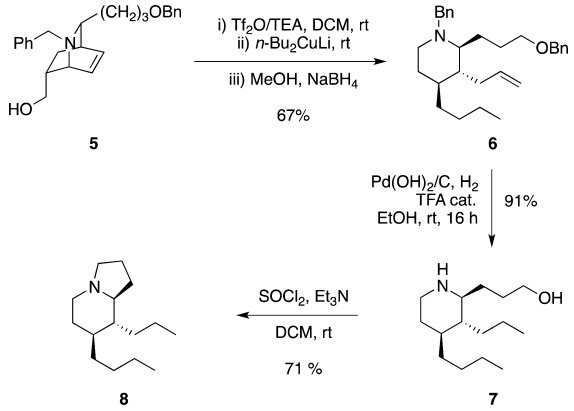
In addition to being highly stereoselective and efficient for a one-pot, three-step sequence, this methodology allows for considerable synthetic flexibility in order to vary the substitution pattern on the piperidine ring at the 2-[12] and 4-positions by the selection of either a Grignard or an organocuprate reagent, respectively. Moreover, the compatibility of vinyl and homoallyl cuprates as nucleophiles ensures potential functionalization at the 3-position. For example, piperidines bearing unsaturation in the 4-position (**2g** and **2j**) were used in a RCM reaction using first-generation Grubbs catalyst, giving access to the bicycles **3** and **4** in 74% and 78% yield, respectively (Scheme 2).

Scheme 2. Derivatization Using the RCM Reaction



Another relevant example illustrating the synthetic utility of this methodology is depicted in Scheme 3. Starting from the known enantioenriched azabicyclo[2.2.2]octene **5** (95% ee),[9b] we achieved the preparation of the chiral non-natural indolizidine **8** through a three-step sequence. Applying our method to **5** using *n*-Bu_2CuLi furnished **6** in 67% yield. The latter was hydrogenated to give the free piperidine **7** that was

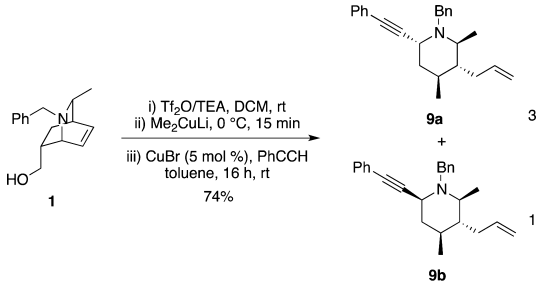
Scheme 3. Synthesis of 7,8-Disubstituted Indolizidine



converted into the corresponding indolizidine **8** via a chlorination/cyclization procedure.[13]

In order to take advantage of the reactivity of the 1,2,3,4-tetrahydropyridine formed in situ after the addition of the organocuprate on the dihydropyridinium intermediate **A**, we applied Knochel's procedure to perform a copper-catalyzed alkyne coupling.[14] Using phenylacetylene in the presence of 5 mol % of CuBr, we obtained the 2,3,4,6-tetrasubstituted piperidine **9** in 74% yield and 3:1 dr (Scheme 4). The diastereoisomers were separated, and the relative configuration of the piperidine substituents was determined by NOE experiments.[15]

Scheme 4. One-Pot Copper-Catalyzed Enamine Coupling

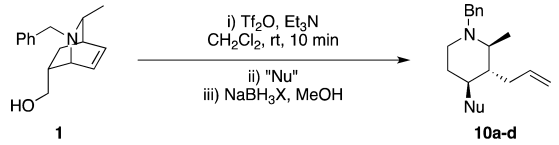


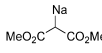
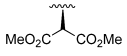
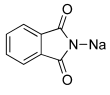
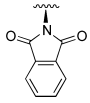
We next examined the reactivity of the dihydropyridinium **A** toward other soft nucleophiles (Table 2). Friedel–Crafts addition was found to occur with *N*-methylindole as nucleophile (entry 1), although the reaction was very slow (72 h for total conversion) and poorly diastereoselective. The sodium salt of dimethyl malonate was added to the 4-position with excellent diastereoselectivity and good yield (entry 2). Interestingly, heteroatom nucleophiles, such as thiophenol (entry 3) and sodium phthalimidate (entry 4), were found to be compatible, although moderate diastereoselectivities were observed.

We envisioned that dihydropyridinium **A** could also act as a reactive dienophile in Diels–Alder reactions using siloxy dienes. Treatment of **1** with 4-phenyl-2-trimethylsilyloxybutadiene led to octahydroisoquinolinone **11** with good overall yield after the sequential reduction with $NaBH_3CN$ and treatment with TFA (Scheme 5). Noteworthy, three stereocenters were installed in one step with high diastereocontrol. The relative configuration was determined by NOE and indicates a stepwise mechanism for the formation of the cyclohexane ring. The silylenol ether

dx.doi.org/10.1021/jo300690h | J. Org. Chem. XXXX, XXX, XXX–XXX

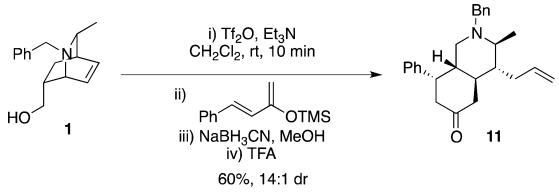
Table 2. Diastereoselective 1,4-Addition of Other Soft Nucleophiles



entry	Nu	R		dr[a]	yield (%)[b]
1[c]			**10a**	2:1	88
2[c]			**10b**	> 19:1	69
3[c]			**10c**	4:1	84
4[d]			**10d**	5:1	57

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Overall yield. [c]X = H. [d]X = CN.

Scheme 5. One-Step Synthesis of Octahydroisoquinolinone



undergoes 1,4-addition, and the resulting enamine then cyclizes through an intramolecular Michael addition.

In order to rationalize the high level of diastereoselectivity observed in the 1,4-addition, we identified the preferred conformation of the dihydropyridinium intermediate **A** by ^{1}H NMR (Figure 1A). The ^{1}H NMR spectrum indicates that no coupling is observed between H^2 and H^3, thus suggesting a dihedral angle $\Phi(H^2{-}C{-}C{-}H^3)$ close to 90°. Based on this

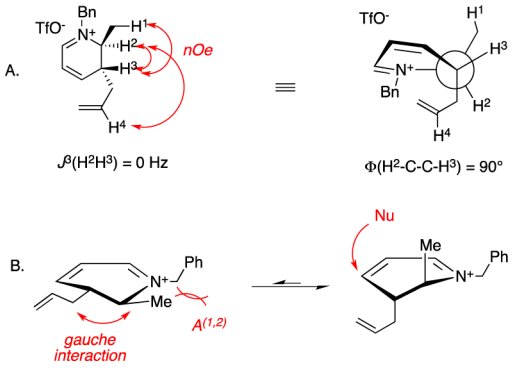


Figure 1. Origin of the Diastereoselectivity.

information and on NOE correlations, we can assume that the alkyl groups are in an axial position in the more stable conformation of the dihydropyridinium. This preferred conformation results from the minimization of both the A-1,2 strain and the gauche interactions that destabilize the other conformer (Figure 1B). The approach of the nucleophiles toward the dihydropyridinium is favored from the opposite face of the allylic group.

In summary, we have developed an efficient and versatile methodology for the stereoselective construction of 2,3,4-trisubstituted 1,2,3,4-tetrahydropyridine core. These compounds can be readily reduced in situ to the corresponding piperidines or used as intermediates for further transformations.

EXPERIMENTAL SECTION

Grob Fragmentation Procedure. To **1** (1 equiv) in CH_2Cl_2 (0.1 N) was slowly added Tf_2O (1.1 equiv). The reaction was stirred at rt for 5 min, and Et_3N (1.2 equiv) was added. This intermediate was directly used as a solution.

General Procedure for Organocuprate Addition. *Method A.* CuI (183 mg, 0.96 mmol) in Et_2O (3.5 mL) was cooled to −78 °C, and the organolithium or organomagnesium (1.92 mmol) was added. The mixture was warmed to rt over 1 h. The dihydropyridinium **A** (from **1**: 97 mg, 0.4 mmol) was added dropwise to the solution of cuprate. The reaction was stirred for 20 min at rt. MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol) were sequentially added. After 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$. The resulting heterogeneous mixture was filtered over Celite, concentrated and purified by chromatography (EtOAc/hexanes/Et_3N 10/89/1) to give **2**.

Method B. CuCN (45 mg, 0.5 mmol) and TMEDA (75 μL, 0.5 mmol) in Et_2O (1 mL) was cooled to −78 °C. The organomagnesium (0.44 mmol) was then added. The mixture was warmed to rt over 1 h and cooled to −78 °C. **A** (from **1**: 49 mg, 0.2 mmol) was added, and the reaction was warmed to rt over 1 h. MeOH (5 mL) and $NaBH_4$ (38 mg, 1.0 mmol) were sequentially added. After 30 min, NaOH 2.0 N (0.5 mL) was added, and the mixture was filtered over Celite. Organic solvents were evaporated. DCM and water were added, products were extracted twice with DCM and dried over $MgSO_4$, solvents were evaporated, and the crude residue was purified by chromatography using Et_3N-treated silica gel (1−10% EtOAc in hexanes) to give **2**.

*rel-(2R,3S,4R)-3-Allyl-1-benzyl-2,4-dimethylpiperidine (**2a**):* 82 mg, 84% yield; gum; ^{1}H NMR δ 7.34−7.27 (m, 4H), 7.25−7.20 (m, 1H), 5.81 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.09−4.98 (m, 2H), 4.06 (d, *J* = 13.5 Hz, 1H), 3.18 (d, *J* = 13.5 Hz, 1H), 2.76 (dt, *J* = 11.7, 3.4 Hz,1H), 2.36−2.23 (m, 2H), 2.18 (dq, *J* = 10.5, 6.0 Hz, 1H), 1.99 (dt, *J* = 2.8, 12.9 Hz, 1H), 1.52−1.45 (m, 1H), 1.39−1.21 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.10 (tt, *J* = 9.8, 4.0 Hz 1H), 0.95 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR δ 139.9, 136.0, 129.2, 128.2, 126.7, 116.1, 59.6, 58.0, 52.5, 48.2, 33.9, 33.8 (2 × C), 20.4, 18.1; HRMS (ESI+) calcd for $[C_{17}H_{26}N + H]^+$ 244.2060, found 244.2063.

*rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-isopropyl-2-methylpiperidine (**2b**):* 47 mg, 87% yield; gum; ^{1}H NMR δ 7.37−7.27 (m, 4H), 7.27−7.20 (m, 1H), 5.80 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.09−4.98 (m, 2H), 4.05 (d, *J* = 13.7 Hz, 1H), 3.24 (d, *J* = 13.6 Hz, 1H), 2.85 (dt, *J* = 11.5, 3.6 Hz,1H), 2.36−2.15 (m, 3H), 2.08−1.93 (m, 2H), 1.48−1.15 (m, 4H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR δ 139.6, 136.0, 129.3, 128.2, 126.8, 116.2, 59.8, 57.9, 52.6, 43.9, 43.3, 33.0, 26.6, 23.0, 21.5, 18.2, 15.6; HRMS (ESI+) calcd for $[C_{19}H_{30}N + H]^+$ 272.2373, found 272.2379.

*rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-butyl-2-methylpiperidine (**2c**):* 47 mg, 83% yield; gum; ^{1}H NMR δ 7.35−7.28 (m, 4H), 7.27−7.20 (m, 1H), 5.81 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.09−4.98 (m, 2H), 4.04 (d, *J* = 13.6 Hz, 1H), 3.23 (d, *J* = 13.6 Hz, 1H), 2.79 (dt, *J* = 12.0, 3.2 Hz,1H), 2.37−2.14 (m, 3H), 1.98 (dt, *J* = 11.5, 2.7 Hz, 1H), 1.64−1.52 (m, 2H), 1.39−1.06 (m, 8H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 139.9, 136.4, 129.2, 128.2, 126.7, 116.0, 59.7,

dx.doi.org/10.1021/jo300690h | J. Org. Chem. XXXX, XXX, XXX−XXX

58.0, 52.1, 45.9, 38.4, 34.0, 33.2, 30.0, 28.5, 23.2, 18.0, 14.3; HRMS (ESI+) calcd for $[C_{20}H_{32}N + H]^+$ 286.2529, found 286.2532.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-isobutyl-2-methylpiperidine (**2d**): 44 mg, 78% yield; gum; ^{1}H NMR δ 7.35−7.28 (m, 4H), 7.26−7.21 (m, 1H), 5.80 (ddt, J = 17.3, 10.4, 7.2 Hz, 1H), 5.09−4.98 (m, 2H), 4.04 (d, J = 13.6 Hz, 1H), 3.26 (d, J = 13.4 Hz, 1H), 2.80 (dt, J = 11.6, 3.5 Hz,1H), 2.38−2.29 (m, 1H), 2.29−2.18 (m, 2H), 2.00 (dt, J = 11.8, 2.8 Hz, 1H), 1.71−1.59 (m, 2H), 1.40 (ddd, J = 13.4, 10.3, 3.2 Hz, 1H), 1.35−1.23 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H), 1.23−1.08 (m, 2H), 0.98 (ddd, J = 13.6, 10.1, 3.2 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 139.5, 136.3, 129.2, 128.2, 126.8, 116.1, 59.7, 57.8, 51.8, 46.6, 43.4, 36.2, 34.0, 30.0, 24.9, 24.5, 21.4, 18.0; HRMS (ESI+) calcd for $[C_{20}H_{32}N + H]^+$ 286.2529, found 286.2532.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-tert-butyl-2-methylpiperidine (**2e**): 43 mg, 75% yield; gum; ^{1}H NMR δ 7.37−7.28 (m, 4H), 7.26−7.20 (m, 1H), 5.75 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 4.96−4.90 (m, 1H), 4.87−4.79 (m, 1H), 3.78 (d, J = 13.5 Hz, 1H), 3.46 (d, J = 13.2 Hz, 1H), 2.68 (ddd, J = 10.8, 6.5, 2.5 Hz,1H), 2.55−2.43 (m, 2H), 2.40−2.30 (m, 1H), 2.23−2.14 (m, 1H), 1.68−1.59 (m, 1H), 1.59−1.46 (m, 1H), 1.39−1.30 (m, 1H), 1.19 (ddd, J = 12.6, 7.4, 5.3 Hz, 1H), 1.10 (d, J = 6.6 Hz, 3H), 0.93 (m, 9H); ^{13}C NMR δ 140.2, 137.8, 129.1, 128.2, 126.8, 115.9, 59.6, 56.3, 49.5, 46.9, 42.5, 40.0, 33.8, 28.7, 23.8, 17.7; HRMS (ESI+) calcd for $[C_{20}H_{32}N + H]^+$ 286.2529, found 286.2525.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-2-methyl-4-phenethylpiperidine (**2f**): 51 mg, 77% yield; gum; ^{1}H NMR δ 7.37−7.21 (m, 7H), 7.21−7.14 (m, 3H), 5.92 (ddt, J = 17.1, 10.0, 7.1 Hz, 1H), 5.07−4.96 (m, 2H), 4.05 (d, J = 13.6 Hz, 1H), 3.22 (d, J = 13.6 Hz, 1H), 2.87−2.78 (m, 1H), 2.70 (ddd, J = 13.7, 11.1, 5.0 Hz,1H), 2.48 (ddd, J = 13.6, 10.5, 5.9 Hz,1H), 2.38−2.15 (m, 3H), 2.06−1.87 (m, 2H), 1.78−1.68 (m, 1H), 1.52−1.40 (m, 1H), 1.40−1.21 (m, 3H), 1.27 (d, J = 6.1 Hz, 3H); ^{13}C NMR δ 143.0, 139.6 (2 x C), 136.1, 129.2, 128.4, 128.2, 126.8, 125.8, 116.2, 59.7, 57.9, 51.9, 45.7, 38.1, 35.6, 33.9, 32.7, 29.9, 17.9; HRMS (ESI+) calcd for $[C_{24}H_{32}N + H]^+$ 334.2529, found 334.2535.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-(but-3-enyl)-2-methylpiperidine (**2g**): 48 mg, 84% yield; gum; ^{1}H NMR δ 7.37−7.27 (m, 4H), 7.27−7.20 (m, 1H), 5.89−5.72 (m, 2H), 5.09−4.90 (m, 4H), 4.04 (d, J = 13.5 Hz, 1H), 3.22 (d, J = 13.5 Hz, 1H), 2.84−2.76 (m, 1H), 2.38−2.07 (m, 4H), 2.04−1.89 (m, 2H), 1.75−1.58 (m, 2H), 1.36−1.14 (m, 4H), 1.26 (d, J = 6.1 Hz, 3H); ^{13}C NMR δ 139.8, 139.3, 136.3, 129.2, 128.2, 126.8, 116.1, 114.4, 59.7, 58.0, 52.0, 45.9, 38.0, 34.0, 32.8, 30.6, 29.8, 18.0; HRMS (ESI+) calcd for $[C_{20}H_{30}N + H]^+$ 284.2373, found 284.2374.

rel-(2R,3S,4R)-3-Allyl-1,4-dibenzyl-2-methylpiperidine (**2h**): 41 mg, 64% yield; gum; ^{1}H NMR δ 7.34−7.22 (m, 7H), 7.22−7.16 (m, 1H), 7.16−7.11 (m, 2H), 5.92 (ddt, J = 17.3, 10.1, 7.2 Hz, 1H), 5.20−5.10 (m, 2H), 4.06 (d, J = 13.6 Hz, 1H), 3.26 (d, J = 13.6 Hz, 1H), 3.16 (dd, J = 13.1, 3.4 Hz,1H), 2.75 (dt, J = 11.8, 3.7 Hz,1H), 2.57−2.48 (m, 1H), 2.47−2.39 (m, 1H), 2.29 (ddd, J = 12.1, 9.4, 5.9 Hz, 1H), 2.17 (dd, J = 13.2, 10.3 Hz,1H), 1.92 (dt, J = 2.6, 13.6 Hz,1H), 1.55 (ddt, J = 21.9, 10.9, 3.9 Hz, 1H), 1.43−1.31 (m, 2H), 1.34 (d, J = 6.0 Hz, 3H), 1.27−1.15 (m, 1H); ^{13}C NMR δ 141.1, 139.5, 136.0, 129.3, 129.2, 128.3, 128.2, 126.8, 125.8, 116.5, 59.6, 57.8, 51.9, 46.2, 40.8, 40.4, 34.1, 29.8, 18.1; HRMS (ESI+) calcd for $[C_{23}H_{30}N + H]^+$ 320.2373, found 320.2380.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-2-methyl-4-((trimethylsilyl)-methyl)piperidine (**2i**): 56 mg, 89% yield; gum; ^{1}H NMR δ 7.38−7.30 (m, 4H), 7.30−7.22 (m, 1H), 5.82 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.12−4.99 (m, 2H), 4.07 (d, J = 13.5 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H), 2.78 (dt, J = 11.6, 3.3 Hz,1H), 2.43−2.33 (m, 1H), 2.31−2.16 (m, 2H), 2.01 (dt, J = 2.5, 13.5 Hz, 1H), 1.71−1.62 (m, 1H), 1.44−1.33 (m, 1H), 1.33−1.11 (m, 2H), 1.30 (d, J = 5.9 Hz, 3H), 0.98 (dd, J = 14.9, 2.6 Hz, 1H), 0.32 (dd, J = 14.8, 10.5 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR δ 139.7, 136.5, 129.2, 128.2, 126.8, 115.9, 60.0, 58.0, 52.2, 49.0, 35.7, 34.2, 33.6, 21.9, 18.2, −0.3; HRMS (ESI+) calcd for $[C_{20}H_{34}NSi + H]^+$ 316.2455, found 316.2461.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-2-methyl-4-vinylpiperidine (**2j**): 52 mg, 51% yield; gum; ^{1}H NMR δ 7.36−7.27 (m, 4H), 7.27−7.20 (m, 1H), 5.79 (ddt, J = 17.5, 10.3, 7.5 Hz, 1H), 5.63 (ddd, J = 19.2, 10.2, 9.0 Hz, 1H), 5.07−4.96 (m, 4H), 4.08 (d, J = 13.5 Hz, 1H), 3.18 (d, J = 13.6 Hz, 1H), 2.79 (dt, J = 11.8, 3.4 Hz, 1H), 2.31−2.25 (m, 2H), 2.25−2.15 (m, 1H), 2.05−1.93 (m, 2H), 1.53−1.41 (m, 2H), 1.35−1.22 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 143.2, 139.8, 135.5, 129.2, 128.3, 126.8, 116.5, 114.7, 59.3, 57.9, 51.9, 45.4, 44.7, 34.1, 31.9, 17.8; HRMS (ESI+) calcd for $[C_{18}H_{26}N + H]^+$ 256.2060, found 256.2066.

rel-(2R,3S,4S)-3-Allyl-1-benzyl-4-cyclopentyl-2-methylpiperidine (**2k**): 25 mg, 42% yield; gum; ^{1}H NMR δ 7.35−7.27 (m, 4H), 7.25−7.20 (m, 1H), 5.80 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.07−4.97 (m, 2H), 3.95 (d, J = 13.6 Hz, 1H), 3.28 (d, J = 13.6 Hz, 1H), 2.80 (ddd, J = 11.7, 4.2, 2.4 Hz,1H), 2.42−2.33 (m, 1H), 2.33−2.14 (m, 3H), 2.07−1.99 (m, 1H), 1.63−1.44 (m, 7H), 1.42−1.12 (m, 5H), 1.24 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 139.9, 136.8, 129.1, 128.2, 126.8, 116.0, 59.1, 58.2, 50.7, 44.5, 41.1, 40.5, 30.2, 27.0, 25.8, 25.7, 24.5, 17.2; HRMS (ESI+) calcd for $[C_{21}H_{32}N + H]^+$ 298.2529, found 298.2528.

rel-(2R,3S,4S)-3-Allyl-1-benzyl-4-cyclohexyl-2-methylpiperidine (**2l**): 43 mg, 69% yield; gum; ^{1}H NMR δ 7.35−7.27 (m, 4H), 7.27−7.19 (m, 1H), 5.80 (ddt, J = 17.0, 10.1, 7.0 Hz, 1H), 5.10−4.99 (m, 2H), 4.05 (d, J = 13.6 Hz, 1H), 3.23 (d, J = 13.6 Hz, 1H), 2.83 (dt, J = 11.6, 3.5 Hz,1H), 2.36−2.14 (m, 3H), 1.98 (dt, J = 11.8, 2.6 Hz, 1H), 1.80−1.71 (m, 2H), 1.71−1.54 (m, 3H), 1.51−1.04 (m, 9H), 1.29 (d, J = 6.3 Hz, 3H), 1.01−0.87 (m, 1H); ^{13}C NMR δ 139.6, 136.2, 129.2, 128.2, 126.7, 116.0, 59.9, 58.0, 52.8, 44.1, 42.6, 38.0, 34.6, 33.3, 33.1, 27.5, 27.1, 26.5, 24.9, 18.2; HRMS (ESI+) calcd for $[C_{22}H_{34}N + H]^+$ 312.2686, found 312.2692.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-2-methyl-4-phenylpiperidine (**2m**): 51 mg, 84% yield; gum; ^{1}H NMR δ 7.40−7.16 (m, 10H), 5.75 (ddt, J = 17.5, 10.4, 7.5 Hz, 1H), 4.99−4.93 (m, 1H), 4.90−4.82 (m, 1H), 4.16 (d, J = 13.6 Hz, 1H), 3.28 (d, J = 13.6 Hz, 1H), 2.89 (dt, J = 11.6, 3.5 Hz,1H), 2.49 (dt, J = 11.7, 4.1 Hz,1H), 2.33 (dq, J = 10.0, 6.1 Hz,1H), 2.21−2.11 (m, 1H), 2.13 (dt, J = 2.7, 11.9 Hz,1H), 1.95−1.85 (m, 1H), 1.83−1.71 (m, 2H), 1.70−1.63 (m, 1H), 1.35 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 145.8, 139.7, 135.2, 129.2, 128.6, 128.3, 127.9, 126.8, 126.2, 116.6, 60.0, 57.8, 53.0, 47.0, 46.3, 34.3, 33.9, 17.9; HRMS (ESI+) calcd for $[C_{22}H_{28}N + H]^+$ 306.2216, found 306.2218.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-(4-chlorophenyl)-2-methylpiperidine (**2n**): 63 mg, 93% yield; gum; ^{1}H NMR δ 7.41−7.31 (m, 4H), 7.31−7.23 (m, 3H), 7.18−7.10 (m, 2H), 5.73 (ddt, J = 17.3, 10.3, 7.3 Hz, 1H), 5.02−4.94 (m, 1H), 4.91−4.82 (m, 1H), 4.16 (d, J = 13.6 Hz, 1H), 3.27 (d, J = 13.6 Hz, 1H), 2.88 (dt, J = 11.7, 3.4 Hz,1H), 2.48 (dt, J = 11.7, 4.2 Hz,1H), 2.38−2.28 (m,1H), 2.22−2.06 (m, 2H), 1.94−1.83 (m,1H), 1.79−1.59 (m, 3H), 1.35 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 144.3, 139.6, 134.9, 131.8, 129.2, 129.2, 128.7, 128.3, 126.9, 116.9, 59.9, 57.8, 52.8, 46.4, 46.2, 34.3, 33.9, 17.9; HRMS (ESI+) calcd for $[C_{22}H_{27}ClN + H]^+$ 340.1827, found 340.1834.

rel-3-((2R,3S,4R)-3-Allyl-1-benzyl-2-methylpiperidin-4-yl)-N,N-bis-(trimethylsilyl)aniline (**2o**): 45 mg, 64% yield; gum; ^{1}H NMR δ 7.38−7.30 (m, 4H), 7.28−7.22 (m, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.90−6.87 (m, 1H), 6.75−6.70 (m, 2H), 5.75 (ddt, J = 17.4, 10.3, 7.4 Hz, 1H), 4.99−4.93 (m, 1H), 4.92−4.84 (m, 1H), 4.16 (d, J = 13.5 Hz, 1H), 3.28 (d, J = 13.5 Hz, 1H), 2.88 (dt, J = 11.8, 3.5 Hz,1H), 2.41 (dt, J = 11.8, 4.2 Hz, 1H), 2.30 (dq, J = 10.0, 5.9 Hz, 1H), 2.23−2.05 (m, 2H), 1.97−1.88 (m, 1H), 1.80−1.67 (m, 2H), 1.66−1.60 (m, 1H), 1.35 (d, J = 6.2 Hz, 3H), 0.04 (s, 18H); ^{13}C NMR δ 148.1, 146.1, 139.5, 135.3, 129.6, 129.3, 128.4, 128.3, 128.1, 126.9, 123.4, 116.6, 60.0, 58.0, 53.0, 46.8, 46.4, 34.4, 33.8, 17.9, 2.2; HRMS (ESI+) calcd for $[C_{22}H_{29}N_2 - 2SiMe_3 + 3H]^+$ 321.2325, found 321.2328.

rel-(2R,3S,4R)-3-Allyl-1-benzyl-4-mesityl-2-methylpiperidine (**2p**): 58 mg, 83% yield; gum; ^{1}H NMR δ 7.40−7.31 (m, 4H), 7.29−7.23 (m, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 5.70 (ddt, J = 17.2, 10.0, 7.1 Hz, 1H), 4.95−4.89 (m, 1H), 4.80−4.72 (m, 1H), 4.12 (d, J = 13.6 Hz, 1H), 3.35 (d, J = 13.6 Hz, 1H), 2.98−2.86 (m, 2H), 2.45 (s, 3H), 2.38−2.15 (m, 5H), 2.29 (s, 3H), 2.24 (s, 3H), 2.06 (dq, J = 12.6, 3.6 Hz,1H), 1.98−1.88 (m, 1H), 1.50−1.42 (m, 1H), 1.36 (d, J = 5.4 Hz, 3H); ^{13}C NMR δ 139.8, 137.7, 137.0, 136.1, 135.7, 135.1, 131.3, 129.6, 129.2, 128.3, 126.8, 116.5, 61.3, 57.3, 53.6, 43.5, 43.3, 34.4, 29.4, 22.2, 21.8, 20.8, 17.9; HRMS (ESI+) calcd for $[C_{25}H_{34}N + H]^+$ 348.2686, found 348.2691.

dx.doi.org/10.1021/jo300690h | J. Org. Chem. XXXX, XXX, XXX−XXX

General Procedure for the Metathesis. To **2g** (28 mg, 0.1 mmol) or **2j** (13 mg, 0.05 mmol) in CH_2Cl_2 (0.03 N) was added 5 mol % of benzylidenebis(tricyclohexylphosphine)dichlororuthenium (Grubbs I) . The mixture was stirred at rt until completion (TLC and MS monitoring). Concentration and purification by chromatography (20% EtOAc in hexanes) gave the desired products as a colorless oil.

*rel-(1R,4aS,7aS)-2-Benzyl-1-methyl-2,3,4,4a,7,7a-hexahydro-1H-cyclopenta[c]pyridine (**3**):* 8 mg, 74% yield; gum; ^{1}H NMR δ 7.35−7.28 (m, 4H), 7.27−7.19 (m, 1H), 5.84−5.75 (m, 2H), 4.10 (d, J = 13.6 Hz, 1H), 3.27 (d, J = 13.6 Hz, 1H), 2.94−2.86 (m, 1H), 2.42−2.25 (m, 2H), 2.12 (dt, J = 11.9, 3.0 Hz, 1H), 2.08−1.99 (m, 1H), 1.96−1.87 (m, 1H), 1.82 (ddd, J = 12.1, 5.4, 2.7 Hz, 1H), 1.56 (ddd, J = 21.4, 11.1, 6.8 Hz, 1H), 1.41 (dq, J = 12.1, 3.7 Hz, 1H), 1.25 (d, J = 5.9 Hz, 3H); ^{13}C NMR δ 139.7, 135.8, 131.3, 129.3, 128.2, 126.8, 60.4, 57.7, 54.8, 53.8, 49.5, 35.0, 30.1, 19.1; HRMS (ESI+) calcd for $[C_{16}H_{22}N + H]^+$ 228.1747, found 228.1750.

*rel-(1R,4aR,9aS,Z)-2-Benzyl-1-methyl-2,3,4,4a,5,6,9,9a-octahydro-1H-cyclohepta[c]pyridine (**4**):* 20 mg, 78% yield; gum; ^{1}H NMR δ 7.35−7.27 (m, 4H), 7.27−7.19 (m, 1H), 5.92−5.80 (m, 2H), 4.05 (d, J = 13.7 Hz, 1H), 3.22 (d, J = 13.5 Hz, 1H), 2.83−2.74 (m, 1H), 2.26−2.17 (m, 1H), 2.17−2.11 (m, 2H), 2.11−2.02 (m, 1H), 2.00−1.82 (m, 2H), 1.68−1.59 (m, 1H), 1.42−1.24 (m, 3H), 1.32 (d, J = 5.8 Hz, 3H), 1.19−1.07 (m, 1H), 1.06−0.96 (m, 1H); ^{13}C NMR δ 139.6, 133.3, 131.5, 129.3, 128.2, 126.8, 60.4, 58.2, 52.6, 47.5, 47.2, 35.1, 33.8, 32.4, 27.2, 19.5; HRMS (ESI+) calcd for $[C_{18}H_{26}N + H]^+$ 256.2060, found 256.2063.

*(2S,3R,4S)-3-Allyl-1-benzyl-2-(3-(benzyloxy)propyl)-4-butylpiperidine (**6**).* Method A using **5** (128 mg, 0.34 mmol) and *n*-BuLi (1.63 mmol) gave **6** (96 mg, 67%): gum; $[\alpha]^{20}_D$ = +36.3 (c 0.67, CH_2Cl_2); ^{1}H NMR δ 7.38−7.18 (m, 10H), 5.81 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.07−4.98 (m, 2H), 4.49 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 3.45 (t, J = 6.2 Hz, 2H), 3.10 (d, J = 13.5 Hz, 1H), 2.76 (dt, J = 11.4, 3.2 Hz,1H), 2.36−2.27 (m, 1H), 2.27−2.18 (m, 2H), 1.96 (dt, J = 11.4, 2.6 Hz,1H), 1.89−1.64 (m, 4H), 1.61−1.59 (m, 2H), 1.44−1.36 (m, 1H), 1.35−1.07 (m, 7H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 140.4, 138.9, 136.3, 128.8, 128.4, 128.2, 127.6, 127.5, 126.7, 116.2, 72.9, 70.9, 63.4, 56.9, 51.5, 41.5, 38.2, 33.7, 33.3, 29.3, 28.6, 25.4, 24.5, 23.2, 14.3; HRMS (ESI+) calcd for $[C_{29}H_{42}NO + H]^+$ 420.3261, found 420.3267.

*3-((2S,3R,4S)-4-Butyl-3-propylpiperidin-2-yl)propan-1-ol (**7**).* Compound **6** (47 mg, 0.11 mmol), $Pd(OH)_2/C$ (10 mol %), and TFA (1 μL, 0.013 mmol) in EtOH were stirred under H_2 overnight. The mixture was filtered, concentrated, and purified by chromatography (94/1/5 EtOAc/NH_4OH/MeOH) to give **7** (26 mg, 99%): gum; $[\alpha]^{20}_D$ +5.8 (c 0.45, CH_2Cl_2); ^{1}H NMR δ 3.9 (bs, 2H), 3.64−3.48 (m, 2H), 3.16−3.04 (m, 1H), 2.60 (dt, J = 12.5, 2.4 Hz,1H), 2.51−2.42 (m, 1H), 1.84−1.69 (m, 3H), 1.64−1.47 (m, 3H), 1.46−1.00 (m, 12H), 0.96−0.79 (m, 6H); ^{13}C NMR δ 62.9, 59.1, 45.9, 44.2, 38.7, 32.8, 32.8, 31.6, 30.8, 29.6, 28.5, 23.2, 18.6, 15.1, 14.2; HRMS (ESI+) calcd for $[C_{15}H_{32}NO + H]^+$ 242.2478, found 242.2484.

*(7S,8R,8aS)-7-Butyl-8-propyloctahydroindolizine (**8**).* $SOCl_2$ (15 μL, 0.20 mmol) was dissolved in CH_2Cl_2. Compound **7** (25 mg, 0.10 mmol) in CH_2Cl_2 was added over 2 h. After 16 h, Et_3N (43 μL, 0.30 mmol) was added, and solution was stirred for 6 h. Saturated aqueous Na_2CO_3 was added, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, concentrated and purified by chromatography (1% MeOH in EtOAc) to give **8** (71%, 16 mg): liquid; $[\alpha]^{20}_D$ +12.5 (c 0.575, CH_2Cl_2); ^{1}H NMR δ 3.06−2.9 (m, 2H), 1.96 (q, J = 9.1 Hz, 1H), 1.90−1.76 (m, 2H), 1.74−1.62 (m, 2H), 1.62−1.48 (m, 2H), 1.48−1.01 (m, 12H), 1.01−0.88 (m, 2H), 0.87−0.66 (m, 6H); ^{13}C NMR δ 68.4, 54.6, 52.8, 45.7, 38.7, 32.4, 31.9, 31.3, 29.5, 28.9, 23.2, 21.0, 18.9, 15.1, 14.3; HRMS (ESI+) calcd for $[C_{15}H_{30}N + H]^+$ 224.2373, found 224.2383.

*rel-(2R,3S,4R,6S)- and rel-(2R,3S,4R,6R)-3-Allyl-1-benzyl-2,4-dimethyl-6-(phenylethynyl)piperidine (**9a,b**).* To **A** (from **1**: 50 mg, 0.20 mmol) was added Me_2CuLi (CuI (84 mg, 0.44 mmol) and MeLi (0.88 mmol)) in Et_2O (2 mL). The reaction was stirred for 20 min at rt and transferred to another flask containing CuBr (1.5 mg, 0.01 mmol) and phenylacetylene (66 μL, 0.60 mmol) in toluene (1 mL). The mixture was stirred 16 h, filtered over Celite, concentrated, and purified by chromatography (EtOAc/hexanes/Et_3N 1/98/1 elution) (51 mg, 74% yield, 3:1 dr). Major diastereoisomer only: rel-(**2R,3S,4R,6S**)-(**9a**)**:** gum; ^{1}H NMR δ 7.52−7.46 (m, 2H), 7.45−7.40 (m, 2H), 7.38−7.30 (m, 5H), 7.28−7.22 (m, 1H), 5.90 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.14−5.02 (m, 2H), 4.13 (d, J = 13.2 Hz, 1H), 3.71−3.65 (m, 1H), 3.44 (d, J = 13.2 Hz, 1H), 2.81−2.71 (m, 1H), 2.40−2.27 (m, 2H), 2.04−1.90 (m, 1H), 1.75 (dt, J = 12.7, 3.3 Hz, 1H), 1.49 (dt, J = 4.3, 12.7 Hz, 1H), 1.25 (d, J = 6.1 Hz, 3H), 1.16−1.03 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 140.1, 136.1, 131.8, 129.2, 128.4, 128.3, 127.9, 126.9, 123.8, 116.1, 88.2, 87.0, 55.5, 55.0, 52.2, 48.6, 38.8, 33.9, 29.3, 20.3, 18.1; HRMS (ESI+) calcd for $[C_{25}H_{30}N + H]^+$ 344.2373, found 344.2379.

General Procedure for Nucleophilic Addition. The dihydropyridinium **A** (from **1**: 1 equiv) was added to a solution of the appropriate nucleophile and the mixture stirred at rt until the addition reaction was completed. MeOH (0.02 N) and $NaBH_4$ (5 equiv) were added, and the mixture was stirred for 30 min. Saturated aqueous $NaHCO_3$ was added. Extraction with CH_2Cl_2, drying over Na_2SO_4, filtration, concentration, and purification by chromatography using triethylamine pretreated silica gel led to the desired compound.

*rel-3-((2R,3S,4R)- and rel-3-((2R,3S,4S)-3-Allyl-1-benzyl-2-methylpiperidin-4-yl)-1-methyl-1H-indole (**10a-10a′**).* The general procedure was followed using **1** (25 mg, 0.1 mmol) and *N*-methylindole (128 μL, 1 mmol). The mixture was stirred for 72 h before the reduction step. Products were purified using 0 to 50% EtOAc in hexanes to give **10a** and **10a′** (32 mg, 88% yield, 2:1 dr) as a yellow gum. Major diastereoisomer only, ***rel*-3-((2*R*,3*S*,4*R*)-10a:** ^{1}H NMR δ 7.68 (d, J = 8.0 Hz, 1H), 7.42−7.17 (m, 7H), 7.08 (t, J = 7.8 Hz, 1H), 6.84 (s, 1H), 5.80 (ddt, J = 17.4, 10.0, 7.4 Hz, 1H), 4.97−4.90 (m, 1H), 4.89−4.81 (m, 1H), 4.17 (d, J = 13.5 Hz, 1H), 3.75 (s, 3H), 3.31 (d, J = 13.4 Hz, 1H), 2.89 (dt, J = 11.7, 3.3 Hz, 1H), 2.78 (dt, J = 3.8, 11.8 Hz, 1H), 2.40−2.31 (m, 1H), 2.25−2.05 (m, 3H), 2.00−1.86 (m, 2H), 1.80−1.72 (m, 1H), 1.35 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 139.7, 137.2, 136.0, 129.3, 128.3, 127.5, 126.9, 126.0, 121.5, 119.7, 119.1, 118.6, 116.3, 109.3, 60.5, 57.8, 53.1, 46.5, 37.8, 34.5, 34.1, 32.8, 18.0; HRMS (ESI+) calcd for $[C_{25}H_{31}N_2 + H]^+$ 359.2484, found 359.2508.

*rel-Dimethyl 2-((2R,3S,4R)-3-Allyl-1-benzyl-2-methylpiperidin-4-yl)malonate (**10b**).* The general procedure was followed with **1** (97 mg, 0.40 mmol), sodium dimethylmalonate (dimethyl malonate (160 μL, 1.40 mmol), and NaH (48 mg, 1.20 mmol) in THF). The mixture was stirred for 14 h before the reduction step. The products were purified using 0−50% EtOAc in hexanes to give **10b** (99 mg, 69% yield, >19:1 dr): gum; ^{1}H NMR δ 7.33−7.26 (m, 4H), 7.25−7.19 (m, 1H), 5.78 (ddt, J = 17.2, 10.0, 7.1 Hz, 1H), 5.11−5.02 (m, 2H), 3.93 (d, J = 13.6 Hz, 1H), 3.80 (d, J = 4.9 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.30 (d, J = 13.6 Hz, 1H), 2.78 (dt, J = 12.0, 4.0 Hz, 1H), 2.42−2.28 (m, 3H), 2.15−2.05 (m, 2H), 1.75−1.57 (m, 2H), 1.54−1.45 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 170.0, 169.3, 139.9, 135.3, 129.2, 128.7, 127.3, 117.4, 59.2, 57.4, 53.2, 52.8, 52.5, 51.0, 42.9, 39.5, 34.3, 26.3, 17.9; HRMS (ESI+) calcd for $[C_{21}H_{30}NO_4 + H]^+$ 360.2169, found 360.2187.

*rel-(2R,3R,4R)- and rel-(2R,3R,4S)-3-Allyl-1-benzyl-2-methyl-4-(phenylthio)piperidine (**10c−c′**).* The general procedure was followed with **1** (97 mg, 0.40 mmol) and benzenethiol (124 μL, 1.20 mmol). The mixture was stirred for 72 h before the reduction step. The products were purified using 0 to 10% EtOAc in hexanes to give the desired products (113 mg, 84% yield, 4:1 dr). Major diastereoisomer only: ***rel*-(2R,3R,4R)-10c:** gum; ^{1}H NMR, δ 7.47−7.40 (m, 2H), 7.36−7.21 (m, 8H), 5.86 (ddt, J = 17.3, 10.0, 7.4 Hz, 1H), 5.21−5.07 (m, 2H), 3.96 (d, J = 13.5 Hz, 1H), 3.30 (d, J = 13.5 Hz, 1H), 3.05 (dt, J = 10.5, 4.6 Hz, 1H), 2.86−2.75 (m, 2H), 2.56−2.38 (m, 2H), 2.08 (dt, J = 11.7, 2.6 Hz, 1H), 1.95−1.85 (m, 1H), 1.79−1.57 (m, 2H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 139.5, 135.2, 134.9, 132.9, 128.9, 128.9, 128.2, 127.1, 126.8, 117.3, 59.2, 57.2, 50.4, 49.1, 45.3, 34.6, 32.0, 17.3; HRMS (ESI+) calcd for $[C_{22}H_{28}NS + H]^+$ 338.1937, found 338.1942.

*rel-2-((2R,3R,4R)-3-Allyl-1-benzyl-2-methylpiperidin-4-yl)-isoindoline-1,3-dione (**10d**).* The general procedure was followed with **1** (49 mg, 0.40 mmol), $NaBH_3CN$ (63 mg, 1.0 mmol) for the reduction step, and sodium phthalimidate prepared from phthalimide (89 mg, 0.6 mmol) and NaH (24 mg, 0.6 mmol) in THF. The mixture

dx.doi.org/10.1021/jo300690h | J. Org. Chem. XXXX, XXX, XXX−XXX

was stirred for 14 h before the reduction step. Products were purified using 0−50% EtOAc in hexanes to give **10d** as a mixture of diastereoisomers (85 mg, 57% yield, 5.25:1 dr). Major diastereoisomer only: gum; ^{1}H NMR δ 7.85−7.81 (m, 2H), 7.74−7.67 (m, 2H), 7.42−7.28 (m, 4H), 7.27−7.21 (m, 1H), 5.82−5.68 (m, 1H), 4.94−4.80 (m, 2H), 4.14−4.03 (m, 1H), 4.08 (d, J = 13.5 Hz, 1H), 3.33 (d, J = 13.6 Hz, 1H), 2.89 (dt, J = 11.8, 3.3 Hz, 1H), 2.59−2.42 (m, 2H), 2.42−2.33 (m, 1H), 2.23 (dt, J = 2.4, 12.4 Hz, 1H), 2.19−2.05 (m, 2H), 1.56−1.47 (m, 1H), 1.33 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 168.6, 139.9, 135.1, 134.0, 132.0, 129.0, 128.3, 126.9, 123.3, 116.5, 59.9, 55.9, 52.9, 51.2, 41.5, 33.9, 28.0, 18.1; HRMS (ESI+) calcd for $[C_{24}H_{27}N_2O_2 + H]^+$ 375.2067, found 375.2076.

*rel-(3R,4S,4aR,8R,8aS)-4-Allyl-2-benzyl-3-methyl-8-phenyloctahydroisoquinolin-6(7H)-one (**11**).* To a flask cooled at 0 °C and containing 2,6-lutidine (232 μL, 2.0 mmol), TMSOTf (220 μL, 1.2 mmol), and styryl methyl ketone (150 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added the dihidropyridinium **A** (from **1**: 97 mg, 0.40 mmol). The resulting mixture was stirred overnight. MeOH (5 mL) and $NaBH_3CN$ (125 mg, 2.0 mmol) were added, and the mixture was stirred for 2 h. TFA (75 μL, 1.0 mmol) was added, the reaction was stirred 30 min, and saturated aqueous Na_2CO_3 was added. The organic layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by chromatography using Et_3N pretreated silica gel (0−60% EtOAc in hexanes) to give **11** (90 mg, 60% yield, 14:1 dr): gum; ^{1}H NMR δ 7.39−7.13 (m, 8H), 6.94−6.79 (m, 2H), 5.73−5.56 (m, 1H), 5.14−4.91 (m, 2H), 4.06 (d, J = 13.6 Hz, 1H), 3.32−3.20 (m, 1H), 3.03 (d, J = 13.6 Hz, 1H), 2.95−2.85 (m, 1H), 2.81 (dd, J = 11.8, 3.1 Hz, 1H), 2.71 (dd, J = 14.6, 7.0 Hz, 1H), 2.66−2.55 (m, 1H), 2.27−2.15 (m, 2H), 2.12−1.86 (m, 3H), 1.73−1.59 (m, 1H), 1.45−1.15 (m, 2H), 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 211.7, 141.4, 139.7, 134.8, 128.9, 128.8, 128.3, 128.2, 126.9, 126.7, 116.9, 59.3, 57.6, 56.8, 47.9, 46.7, 45.9, 45.0, 41.3, 36.7, 32.9, 17.9; HRMS (ESI+) calcd for $[C_{26}H_{32}NO + H]^+$ 374.2478, found 374.2483.

■ ASSOCIATED CONTENT

Supporting Information

Optimization experiments and NMR spectrum for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andre.charette@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), the Canada Research Chairs Program, the Canada Foundation for Innovation, The Centre in Green Chemistry and Catalysis (CGCC), and Université de Montréal.

■ REFERENCES

(1) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, *6*, 633. (d) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191.

(2) For examples, see: (a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679. (b) Vazzana, I.; Budriesi, R.; Terranova, E.; Ioan, P.; Ugenti, M. P.; Tasso, B.; Chiarini, A.; Sparatore, F. *J. Med. Chem.* **2007**, *50*, 334. (c) Satoh, A.; Sagara, T.; Sakoh, H.; Hashimoto, M.; Nakashima, H.; Kato, T.; Goto, Y.; Mizutani, S.; Azuma-Kanoh, T.; Tani, T.; Okuda, S.; Okamoto, O.; Osaki, S.; Iwasawa, Y.; Ohta, H.; Kawamoto, H. *J. Med. Chem.* **2009**, *52*, 4091. (d) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.

(3) For recent reviews, see: (a) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198. (b) Cossy, J. *Chem. Rec.* **2005**, *5*, 70. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (e) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (f) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.

(4) (a) Coombs, T. C.; Lushington, G. H.; Douglas, J.; Aube, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2734. (b) Fernández-Ibáñez, M. A.; Maciá, B.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9339. (c) McLaughlin, N. P.; Evans, P. *J. Org. Chem.* **2010**, *75*, 518. (d) Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4982. (e) Chen, Y.; Zhong, C.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2009**, *11*, 2333. (f) Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473. (g) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012. (h) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222. (i) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336.

(5) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222.

(6) Xiong, X.-F.; Zhang, H.; Peng, J.; Chen, Y.-C. *Chem.—Eur. J.* **2011**, *17*, 2358.

(7) Bates, R. W.; Shuyi Ng, P. *Tetrahedron Lett.* **2011**, *52*, 2969.

(8) Schneider, C.; Börner, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1999**, *1999*, 3353.

(9) For recent publications, see: (a) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830. (b) Lemonnier, G.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 7465. (c) Lemire, A.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 2077. (d) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398. (e) Barbe, G.; St-Onge, M.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5497.

(10) For the preparation of enantioenriched and racemic azabicyclo[2.2.2]octene **1**, see ref 9b and also: (a) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873. (b) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773.

(11) See the Supporting Information for detailed optimization experiments.

(12) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

(13) Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2008**, *73*, 312.

(14) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 2797.

(15) See the Supporting Information for details.