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Divergent Enantioselective Synthesis of (−)-Galanthamine and (−)-Morphine

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Abstract: An efficient divergent synthetic strategy for the synthesis of the opiate and *amaryllidaceae* alkaloids emerges by employing a Pd-catalyzed asymmetric allylic alkylation (AAA) to set the stereochemistry. Three generations of syntheses of galanthamine are discussed in detail with particular focus on the scope of the palladium-catalyzed AAA reactions and intramolecular Heck reactions. The pivotal tricyclic intermediate is available in six steps from 2-bromovanillin and the monoester of methyl 6-hydroxycyclohexene-1-carboxylate. This intermediate requires only two steps to convert to (−)-galanthamine. Using a Heck vinylation, we found that the fourth ring of codeine/morphine could be formed. The final ring formation involves a novel visible light-promoted hydroamination. Thus, six steps are required to convert the pivotal tricyclic intermediate into codeine, which has been demethylated in high yield to morphine.

Introduction

Galanthamine (**1**; Figure 1),[1,2] the parent member of the galanthamine-type *amaryllidaceae* alkaloids (e.g. **1**−**3**), is a centrally acting reversible inhibitor of acetylcholinesterase (Ache), which significantly enhances cognitive functions of Alzheimer's patients.[3−8] It was first approved in Austria and most recently in the rest of Europe and United States for the treatment of Alzheimer's disease. In the endeavor of searching for more potent inhibitors of Ache, there is considerable interest in derivatives which are based on (−)-galanthamine as a lead structure[9,10] since (−)-galanthamine is less toxic than other Ache inhibitors, such as physostigmine and tacrine.[9,11−13] Among them, galanthamine derivatives **4** [12−14] and its iminium salt, synthesized by selective *N*-demethylation followed by *N*-alkylation of galanthamine,[15] were found to be more potent (up to 70-fold) than galanthamine in inhibiting Ache.

Because of the limited supplies and the high cost of its isolation from natural sources,[16,17] several syntheses have been reported using biomimetic oxidative phenol coupling[17−31] to create the critical spiro quaternary carbon of narwedine (**2**), which is converted into **1** by diastereoselective reduction.[16] We disclosed the first enantioselective synthesis of (−)-**1** using a sequential palladium-catalyzed asymmetric allylic alkylation (AAA) and intramolecular Heck cyclization.[32,33] At the same time, several other groups utilized similar Heck cyclizations to construct the quaternary carbon center of (±)-3-deoxygalanthamine[34,35] and (±)-galanthamine **1**.[36] Up to now, however, syntheses employing the oxidative phenol coupling step have

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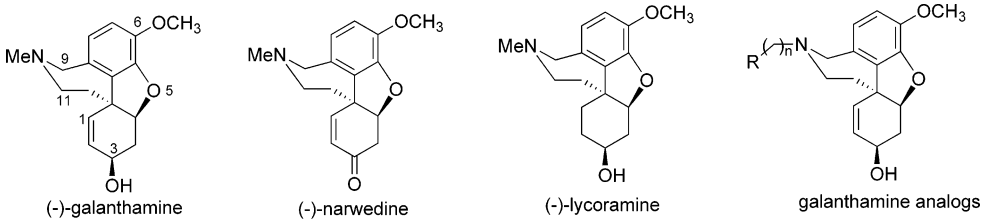

Figure 1. Naturally occurring galanthamine-type *amaryllidaceae* alkaloids and their derivatives.

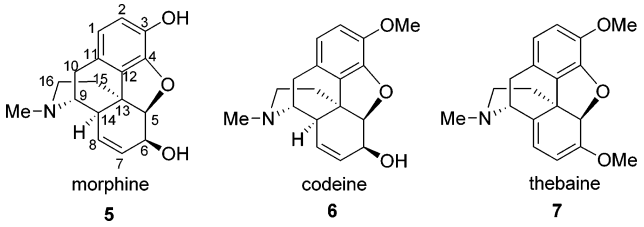

Figure 2. Naturally occurring opium alkaloids.

not been reported to be able to allow direct access to galanthamine derivative **4**.

(−)-Morphine (**5**; Figure 2) is one of the first medicines used by humankind. Since the first documented use of opium in 1500BC, its impact on society has been extremely significant.[37−41] This significance rests on the potency of the active principles, notably, the major one, morphine, which gives it its analgesic, euphoric, and potentially addictive properties. Morphine **5** is the major component of opium, representing 10−15% of its dry weight. Other morphine derivatives, such as codeine (**6**; 3−4%) and thebaine (**7**; 0.1−2%), are also present in opium. The majority of isolated morphine is used to manufacture codeine **6** by simple phenolic methylation.[37] To date, no synthetic drugs or naturally occurring compound has been found which can match the broad spectrum analgesic properties of opium alkaloids. (−)-Morphine **5**, (−)-codeine **6**, (−)-thebaine **7**, and simpler morphinan and benzomorphan structural analogues[42] have broad spectrum pharmacological properties (antitusive, analgesic, and sedative, etc) and are employed in diverse therapies.

Recent investigations have shown that morphine and its cogeners are produced not only in plants but also in mammalian organisms along essentially analogous pathways.[43−47] It has been demonstrated that human cells can synthesize morphine, and it is present in human cells at a nanomolar level.[48] The precise role of endogeneous morphine is not clear. However, there are studies suggesting that morphine may play a general role in immune, vascular, and nervous systems of mammals.[49−54]

The structure−activity relationships of morphine analogues have been studied extensively.[37,55−59] Minor modification of morphine can yield opiates with altered receptor affinities and fundamentally different pharmacologies. Oxymorphone (**8a**), etorphine (**9**), and buprenorphine (**10**) are more potent μ-agonists than morphine.[60,61] Structurally related morphine antagonists (i.e. naloxone (**8b**), naltrexone (**8c**), and nalmefene (**11**)) are used for the treatment of alcohol abuse and eating disorders.[37,55] However, very few compounds made to date from modifications around the phenanthrene structure of morphine have exceeded the pain control properties of morphine without a concomitant increase in addiction potential.[62] Most of these synthetic opiates (Figure 3) are derived from semisyntheses, whereby the natural opium alkaloids are isolated and modified. Clearly, an efficient enantioselective synthesis of morphine will open the way to the preparation of a variety of new morphine analogues.

Divergent Synthetic Plan for Opium Alkaloids and Galanthamine-Type *Amaryllidaceae* Alkaloids

Morphine **5** and galanthamine **1** share the same tricyclic core, and biosynthetically both derive from oxidative phenol couplings (Scheme 1 and Scheme 2).[37,39,44,63−65] These processes were initially proposed on theoretical grounds by Barton.[18,66] It has been shown that the 4′-*O*-methylnorbelladine (**12**) was the precursor for the production of *N*-demethylnarwedine (**15**), presumably through spontaneous cyclization of a hypothetical dienone **14** generated from the oxidative phenol coupling

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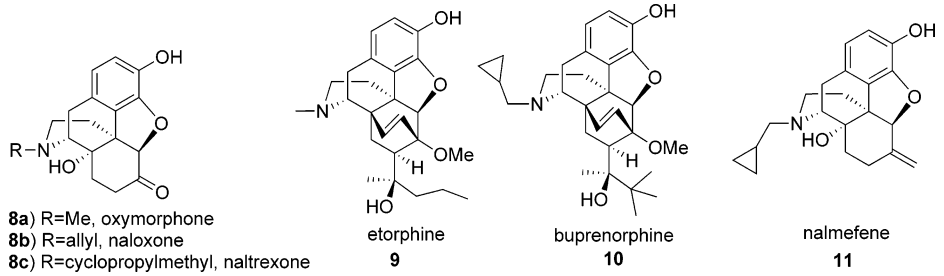
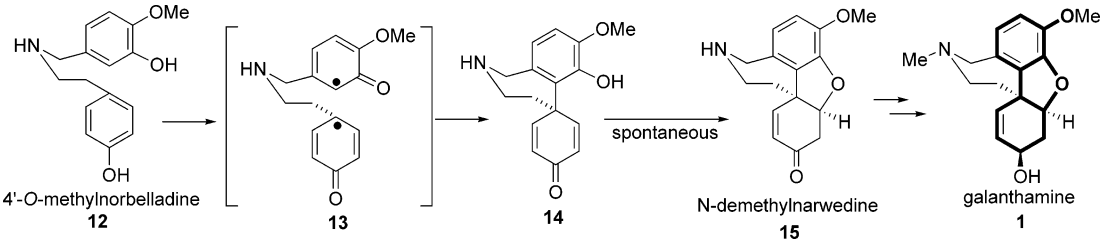
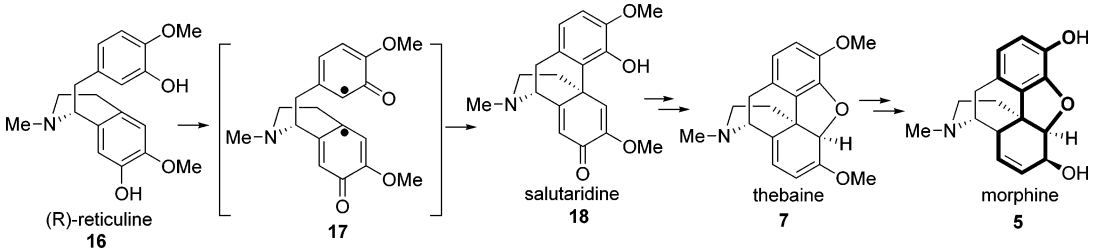


Figure 3. Semisynthetic opiates.

Scheme 1. Biosynthesis of Galanthamine via Oxidative Bisphenol Coupling



Scheme 2. Biosynthesis of Morphine via Oxidative Bisphenol Coupling



(Scheme 1).[63] In plants, the intramolecular ortho−para bisphenolic coupling of (*R*)-reticuline (**16**) is catalyzed by salutaridine synthase, a microsomal NADPH-dependent cytochrome P-450 enzyme. Cyclization of salutaridine (**18***)* to thebaine **7** requires two more enzymes (Scheme 2).[67−71]

The biosyntheses of galanthamine and morphine have inspired many biomimetic syntheses of both amaryllidaceae[16−18,20,21,24−29,72−76] and opium[37,39,77−82] alkaloids. The biomimetic synthesis of galanthamine involving a dynamic resolution has been performed on a pilot scale.[17] The biomimetic synthesis of morphine generally suffered from low yields due to low selectivity of the bisphenol oxidative coupling. The desired para−ortho coupling is complicated by three other possible couplings (ortho−ortho, ortho−para, para−para). However, some bioanalogous syntheses involving Grewe-type cyclization catalyzed by acid[83−95] or palladium[96,97] have led to several successful syntheses.

The distinct difference between the oxidative phenol coupling precursors (bisphenols **12** and **16**) seems to prevent any possibility of accessing these two families of alkaloids from the same advanced intermediate through a biomimetic approach. Indeed, no divergent approach to both families of alkaloids has been realized despite their biogenetic similarity and significant biological activities. Furthermore, despite the extensive synthetic work devoted to these two families of alkaloids and recent

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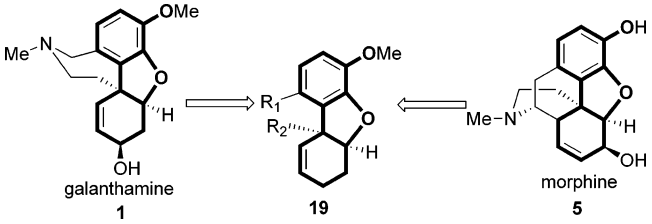
Scheme 3. Divergent Synthetic Plan



progress in the development of enantioselective reactions, only one asymmetric synthesis of galanthamine **1** [98] and two of morphine **5** [96,99] without using resolution were reported prior to our investigation.[32,33,100] The similarity of galanthamine **1** and morphine **5**, as highlighted in Scheme 1 and Scheme 2, arising from oxidative phenol coupling followed by formation of an ether bridge, prompted us to examine the possibility of accessing these products from a common intermediate through chemical synthesis. We envisioned that both alkaloid families could be derived from a common intermediate **19** (Scheme 3), bearing the common tricyclic core of both families of alkaloids and appropriately functionalized side chains (R_1 and R_2) that can be transformed to the additional rings of galanthamine **1** and morphine **5**. Stereoselective formations of two distinct allylic alcohols in galanthamine **1** and morphine **5** from a simple olefin in common intermediate **19** requires careful synthetic planning and conformational analysis.

First Generation Synthesis of Galanthamine

The retrosynthetic analysis of galanthamine begins with removal of the C3 hydroxyl group of galanthamine furnishing 3-deoxygalanthamine (**20**; Scheme 4), which may be directly converted to the natural product by allylic oxidation.[32,101] Tertiary amine **20** could in turn be prepared from dialdehyde **21** by a reductive amination with methylamine. An intramolecular Heck reaction was envisioned to forge the quaternary center in the dialdehydes **21**. This strategy has the potential pitfall that palladium-catalyzed ionization of the phenols may be competitive with the Heck cyclization. To avoid problems of isomerization of the olefin into conjugation with the aldehyde, aryl ether **22** would have an R-group which could readily be converted into the required aldehyde of **21** after the Heck reaction. Finally, the enantioselective synthesis of aryl ether **22**, from which the remaining stereocenters of galanthamine would derive, would be accomplished by a palladium-catalyzed AAA of an ortho-substituted halophenol **24** with cyclohexenyl carbonate **23**.

The *o*-iodo and -bromophenols are both readily prepared from isovanillin (**25**; Scheme 5). Bromination of isovanillin in the presence of a catalytic amount of iron afforded bromophenol **26**.[102] Alternatively, reaction of isovanillin with iodine monochloride produced *o*-iodophenol **27**.[102]

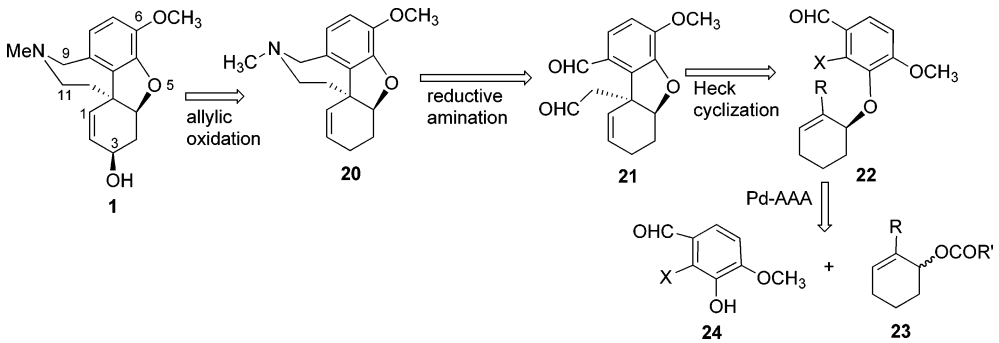
In accordance with our retrosynthetic analysis, the 2-allylcyclohexenol (**30**; Scheme 6) was prepared since the allyl group could be readily converted to the necessary aldehyde by oxidative cleavage. Cyclohexenol **30** prepared by Birch reduction[103] followed by Luche reduction[104] was transformed into the required allyl carbonate (**31** and **32**) and more reactive allyl chloride **33** using standard procedures. Chemoselective osmium tetroxide catalyzed dihydroxylation of carbonate **32** afforded a 1:1 mixture of diastereomeric diols, which was readily protected as the acetonide **34** by treatment with dimethoxymethane in the presence of catalytic *p*-toluenesulfonic acid.

Alternatively, the cyclohexene R-group of intermediate **22** could be an ester. A practical synthesis of esters **38** and **39** utilized the Horner−Wadsworth−Emmons reaction of dialdehyde.[32,105] Reaction of glutaraldehyde **35** with trimethyl phosphonoacetate (**36**) in aqueous potassium carbonate produced alcohol **37** in 46% yield (Scheme 6). Conversion of alcohol **37** to its methyl ester **38** or trichloroethyl carbonate (Troc) **39** was accomplished by treatment with corresponding chloroformate. Direct treatment of crude alcohol **37** with trichloroethyl chloroformate provided the desired carbonate **39** with a slightly higher yield (54%).[33]

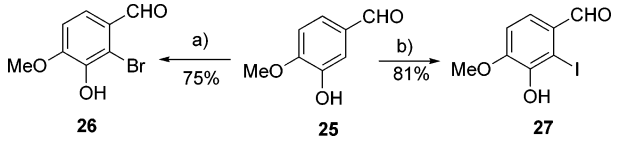
Since there are very few examples of palladium-catalyzed allylic alkylation utilizing ortho-disubstituted phenols,[106,107] the AAA of iodiophenol **27** with cyclohexene methyl carbonate (**40**) was investigated as a test system (Table 1). In the presence of the standard chiral ligand **42**, phenol **27** showed good reactivity producing aryl ether **41** in 75% yield, however, with lower enantioselectivity (66%ee) than that observed in the palladium-catalyzed AAA of simpler phenols and carbonate **40**.[106,107] Confident that phenol **27** would participate as a nucleophile, more complicated carbonates were investigated and the enantioselectivity of this model reaction was not optimized further.

The 2-allylcyclohexenyl carbonates were the first set of substrates examined in the palladium-catalyzed AAA of iodophenol **27** (Table 1). The palladium-catalyzed reaction of phenol **27** with methyl carbonate **31** did not produce any of the desired aryl ether even when the reaction mixture was heated at 40 °C. Similarly, the more reactive carbonate **32** did not react with phenol **27** under the typical conditions of the palladium-catalyzed AAA. Finally, switching to allylic chloride **33** did produce some of the desired ether **43** in poor yield and with no enantioselectivity. Carrying out the reaction in the absence of the palladium catalyst indicated that aryl ether **43** was formed

Scheme 4. Retrosynthetic Analysis of (−)-Galanthamine



Scheme 5. Preparation of the *o*-Halophenols[a]

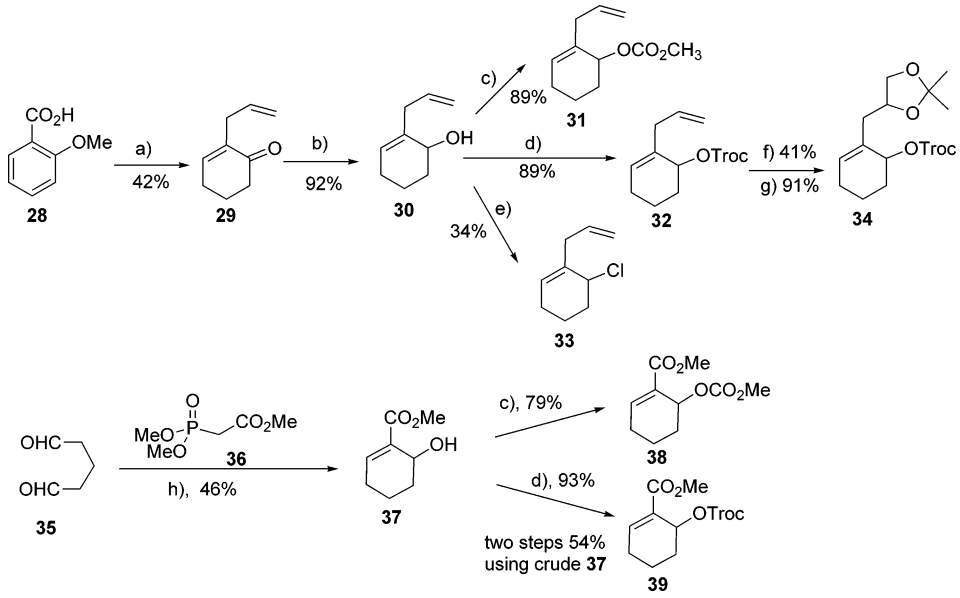


[a] Conditions: (a) Br_2, NaOAc, HOAc, Fe, rt; (b) ICl, pyr.

as a result of a slow uncatalyzed reaction. We postulated that the poor reactivity of 2-allylcyclohexenyl carbonates may result from the 1,4-diene acting as a ligand for palladium. To prevent this coordination, acetonide **34** and ester **38** were examined as substrates (Table 1). Palladium-catalyzed reaction of iodophenol **27** and carbonate **34** failed to produce any of the desired cyclohexenyl ether with both tri-(dibenzylidideneacetone)palladium(0) and bis[π-allylpalladium-(II) chloride] as catalyst precursors. Employing ester **38** as a substrate also resulted in unsuccessful reaction with phenol **27**.

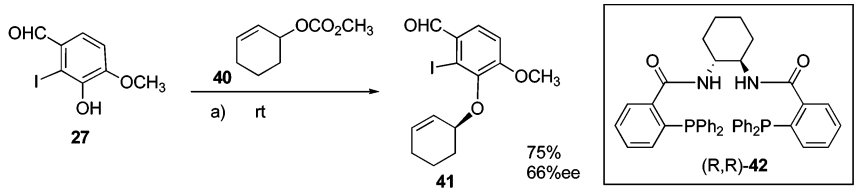
The failure of 2-substituted cyclohexenyl carbonates to participate in palladium-catalyzed AAA with iodophenol **27** prompted us to reexamine their reactivity with simple 4-methoxyphenol (**44**; Scheme 7). 2-Allyl-substituted carbonate **31** did

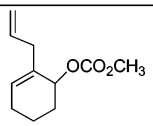
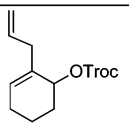
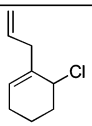
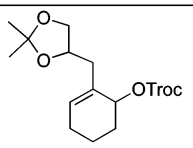
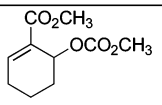
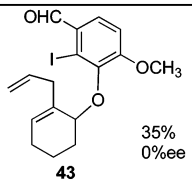
Scheme 6. Synthesis of 2-Substituted Cyclohexenyl Carbonates[a]



[a] Conditions: (a) (i) Na, NH_3/THF; (ii) allyl bromide; (iii) H_2SO_4, H_2O; (b) $NaBH_4$, $CeCl_3$, MeOH/CH_2Cl_2; (c) CH_3O_2CCl, DMAP Pyr, CH_2Cl_2; (d) Troc-Cl, DMAP, Pyr, CH_2Cl_2; (e) CH_3SO_2Cl, Pyr, CH_2Cl_2; (f) 4mol % OsO_4, NMO, CH_2Cl_2, rt, 4 h; (g) $(CH_3O)_2CH_2$, TsOH, acetone, rt, 1 h; (h) K_2CO_3, H_2O, 2 days.

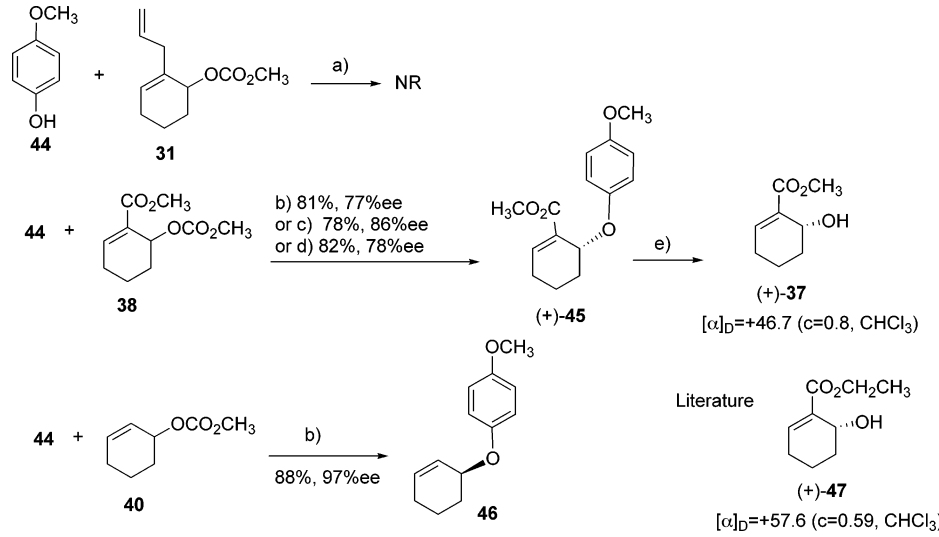
Table 1. Palladium-Catalyzed AAA of Iodophenol **27** with Cyclohexenyl Carbonate or Chloride[a]



Allyl carbonates or allyl chloride	 31	 32	 33	 34	 38
Conditions	a), 40 °C	a), RT	a), 40 °C, Cs_2CO_3	a), 40 °C Cs_2CO_3 or b)	a), 40 °C Et_3N
Product	NR (no reaction)	NR	 43 35% 0%ee	NR	NR

[a] Conditions: (a) 1 mol % Pd_2dba_3, 3 mol % (*R*,*R*)-**42**, CH_2Cl_2; (b) 1 mol % [(η^3-C_3H_5)PdCl]$_2$, 3 mol % (*R*,*R*)-**42**, TEA, CH_2Cl_2, 40 °C.

Scheme 7. Pd-Catalyzed AAA of 4-Methoxyphenol with 2-Substituted Cyclohexenyl Carbonates[a]



[a] Conditions: (a) 1 mol % Pd_2dba_3, 3 mol % (*R,R*)-**42**, Cs_2CO_3, CH_2Cl_2, 40 °C; (b) 1 mol % Pd_2dba_3, 3 mol % (*R,R*)-**42**, CH_2Cl_2, rt; (c) 1 mol % Pd_2dba_3, 3 mol % (*R,R*)-**42**, CH_2Cl_2, 0 °C; (d) 1 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 3 mol % (*R,R*)-**42**, TEA, CH_2Cl_2, 0 °C; (e) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O.

not react with phenol **44** under the typical palladium-catalyzed AAA conditions. Carrying out the reaction in the presence of base, cesium carbonate, and increasing the temperature to 40 °C still failed to produce any of the desired coupling product. On the other hand, the palladium-catalyzed AAA of phenol **44** with ester **38** proceeded smoothly under the typical conditions, affording aryl ether **45** in 81% yield and 77% ee. Lowering the temperature to 0 °C increased the enantiomeric excess to 86% without affecting the yield. The absolute stereochemistry of aryl ether **45** was tentatively assigned by ceric ammonium nitrate (CAN) deprotection of the 4-methoxyphenol to produce alcohol **37** (Scheme 7). Comparison of the rotation of methyl ester **37** to the known ethyl ester **47**, prepared by enzymatic resolution,[108,109] suggested that the stereochemistry of ether **45** is (*R*). Surprisingly, this stereochemistry is opposite to the absolute stereochemistry obtained when unsubstituted cyclic allyl carbonates (e.g. **40**) are used as electrophiles in the palladium-catalyzed AAA of phenols with ligand **42** (Scheme 7).[106,107]

The absolute stereochemistry of **45** is also opposite to that which would be predicted by the mnemonic established for ligand **42**.[107,110,111] A possible explanation for this unexpected reversal is shown in Scheme 8. In the unsubstituted cyclohexenyl π-allyl palladium complex, the palladium cants away from the C2-allyl carbon. Addition of phenol to the π-allyl palladium complex occurs *anti*-periplanar to the palladium through the open region of the chiral space (the right front quadrant depicted in cartoon **48**). In the case of ester-substituted cyclohexenyl π-allyl palladium complex, coordination of the ester to the palladium would result in canting of the C2 carbon toward the palladium.[112,113] If this is the case, for nucleophilic addition to remain *anti*-periplanar to palladium and to occur through an open region of the chiral ligand requires that the nucleophile approach from the left rear quadrant of **48** rather than the front right quadrant. In other words, for addition to occur from the front quadrant, a 180° rotation with respect to the chiral ligand of the π-allyl (see **49**) is required. Nucleophilic addition to ester-substituted cyclohexenyl π-allyl palladium complex, as depicted in **49**, results in the formation of opposite stereochemistry to what is predicted from mnemonic. Interestingly, this reversal in stereochemistry was not observed when acyclic 2-ester-substituted allylic carbonate, acyclic 2-cyano-substituted allylic carbonate, or cyclic 2-cyano-substituted allylic carbonate was utilized as substrate for the AAA reaction of phenol with the same ligand.[114,115] In the case of cyclic 2-cyano-substituted allylic carbonate, which is electronically similar to the ester, the nitrile is geometrically constrained from coordinating to the palladium metal. Similarly, acyclic 2-cyano-substituted allylic carbonate underwent normal allylic alkylation through a *syn*-π-allyl complex. Generally, the *syn*-π-allyl complex is more stable than the *anti*-π-allyl complex due to unfavorable A ^{1,3} strain in the anti complex.[116,117] However, A ^{1,2} steric interaction destabilizes the 2-substituted *syn*-π-allyl complex, and the *anti*-π-allyl become favored as the size of the 2-substituents increases (Scheme 8). The absolute stereochemistry of the products from the *anti*-π-allyl complex is opposite to that from the *syn*-π-allyl complex. In the case of acyclic 2-ester-substituted allylic carbonate, the combination effect of ester coordination to

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(99) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250.
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(110) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
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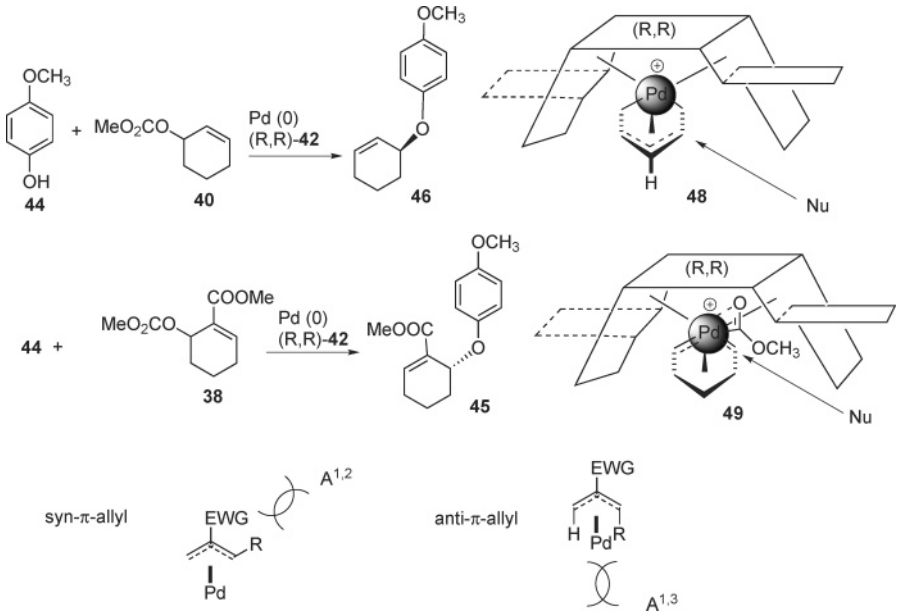
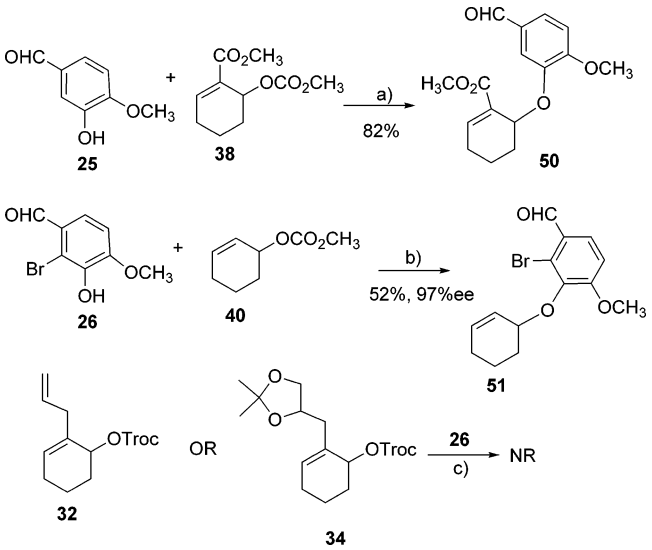
Scheme 8. Rationalization of Reversal in Enantioselectivity



Scheme 9. Pd-Catalyzed Allylic Alkylation of Phenol **25** and Bromophenol **26**[a]



[a] Conditions: (a) 1 mol % Pd_2dba_3, 3 mol % *rac*-**42**, CH_2Cl_2, rt; (b) 1 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 3 mol % (*R*,*R*)-**42**, TEA, CH_2Cl_2, rt; (c) 2.5 mol % Pd_2dba_3, 7.5 mol % (*R*,*R*)-**42**, TEA, CH_2Cl_2, 40 °C.

palladium metal and formation of unusual *anti*-π-allyl was proposed to explain its difference from cyclic 2-ester-substituted allylic carbonate.[115]

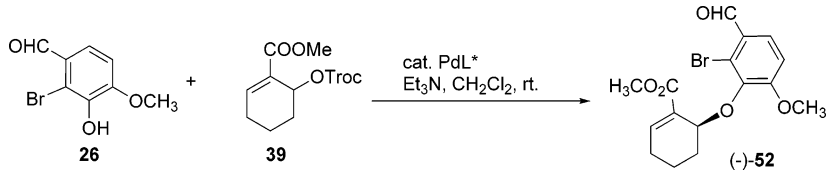
The successful reactions of 4-methoxyphenol **44** with ester-substituted carbonate **38** (Scheme 7) and of iodophenol **27** with unsubstituted carbonate **40** (Table 1) led us to conjecture that the failure of iodophenol **27** to react with **38** (Table 1) is due to steric interaction between the *o*-iodo substituent and the center carbon of the π-allyl. Indeed, palladium-catalyzed reaction of uniodinated vanillin **25** with carbonate **38** produced aryl ether **50** in 82% yield (Scheme 9). The successful reaction of isovanillin **25** with carbonate **38** is consistent with the hypothesis that the failure of iodophenol **27** to react with 2-ester-substituted carbonate **38** is due to the presence of the sterically demanding *o*-iodo group. Since bromide is significantly smaller than iodine, *o*-brominated phenol **26** was examined as a nucleophile (Scheme 9). Palladium-catalyzed AAA reaction of bromophenol **26** with unsubstituted cyclohexenyl carbonate **40** proceeded smoothly to afford aryl ether **51** with excellent enantioselectivity. Unfortunately, as was the case with iodophenol **27** (Table 1) and 4-methoxyphenol **44** (Scheme 7), the palladium- catalyzed reaction of bromophenol **26** with allyl-substituted carbonate **32** failed to produce any aryl ether. Similarly, bromophenol **26** did not react with cyclohexenyl carbonate **34** even at 40 °C.

Unlike the reaction of iodophenol **27** (Table 1), palladium-catalyzed AAA reaction of bromophenol **26** and 2-ester-substituted carbonate **39** in the presence of the standard ligand (*R*,*R*)-**42** proceeded smoothly, affording aryl ether **52** in 60% yield and 71% ee (entry 1, Table 2). The absolute stereochemistry of aryl ether **52** is assumed as shown on the basis of an analogy to aryl ether **45**, and this was confirmed by the optical rotation of the synthetic natural (−)-galanthamine. Variation of the ligand showed that the stilbene diamine ligand **55** provided slightly higher enantioselectivity (entry 4). Switching the palladium source to bis[π-allylpalladium(II) chloride] increased the enantioselectivity to 85% (entry 5). Lowering the catalyst loading to 1% of bis[π-allylpalladium(II) chloride] further increased the enantiomeric excess of aryl ether **52** to 88% (entry 6).

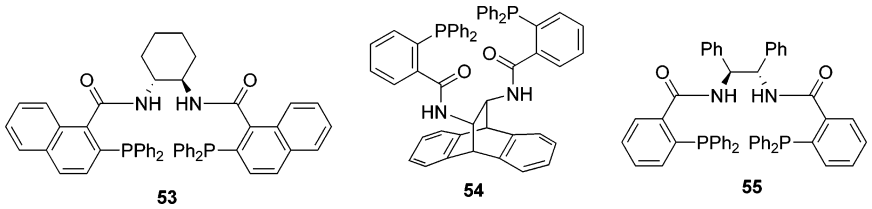
Having prepared the required chiral *o*-haloaryl ethers, we next examined the intramolecular Heck reaction. Larock reported that the Heck reaction of aryl allyl ethers often suffers from competing palladium-catalyzed ionization of the aryloxy group.[118] However, the Heck reaction of *o*-iodoaldehyde **41** (Table 1) proceeded smoothly to afford an inseparable 3:1:1 mixture benzofuran **56a**:**56b**:**56c** products in 82% yield (Scheme 10). The relative stereochemistry of the major product **56a** was assigned by NOE experiments. Since benzofuran **56a** was not useful for the galanthamine synthesis, this Heck reaction was not optimized. Since we can prepare aryl ether **52** with good enantioselectivity in good yield, we thus turned our attention

(118) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687.

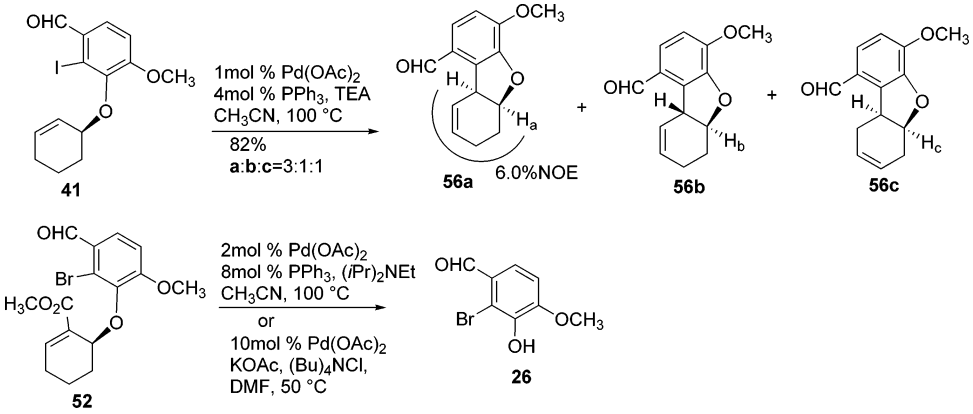
Table 2. Palladium-Catalyzed AAA Reaction of Bromophenol **26** and Carbonate **39**



entry	Pd source	ligand[a]	yield (%)	ee (%)
1	2.5 mol % Pd_2dba_3	7.5 mol % (*R*,*R*)-**42**	60	(+)-71
2	2.5 mol % Pd_2dba_3	7.5 mol % (*R*,*R*)-**53**	61	(+)-47
3	2.5 mol % Pd_2dba_3	7.5 mol % (*S*,*S*)-**54**	27	0
4	2.5 mol % Pd_2dba_3	7.5 mol % (*S*,*S*)-**55**	64	(−)-77
5	2.5 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$	7.5 mol % (*S*,*S*)-**55**	73	(−)-85
6	1 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$	3 mol % (*S*,*S*)-**55**	72	(−)-88



Scheme 10. Intramolecular Heck Reaction of Cyclohexyl Aryl Ether **41** and **52**

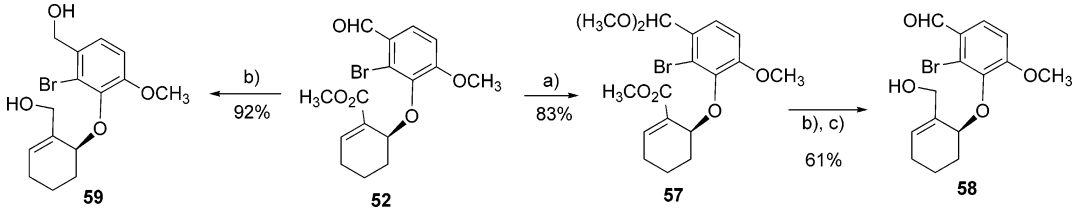


to the Heck reaction of chiral aryl ether **52** (Scheme 10). The reaction conditions utilized for the Heck reaction of unsubstituted cyclohexenyl ether **41** resulted exclusively in ionization of the phenoxy moiety to produce phenol **26**. Larock had reported that the use of Jeffery-type conditions favored the Heck cyclization over ionization.[118] However, even under Jeffrey conditions (10% $Pd(OAc)_2$, KOAc, $(Bu)_4NCl$, dimethylformamide (DMF)) no Heck product was observed. Clearly, the presence of the ester on the olefin is detrimental to the Heck reaction. It should retard the rate of the reaction for both steric (formation of a quaternary versus a tertiary center) and electronic (a contraelectronic carbopalladation is required) reasons. Since the synthesis of galanthamine requires the formation of a quaternary center, the former cannot be avoided. However, the electronic nature of the olefin can be readily changed by reduction of the ester to the corresponding alcohol. The aromatic aldehyde can impose competing effects on the course of the Heck reaction. The presence of the electron-withdrawing aldehyde should increase the rate of oxidative addition of palladium(0) into the aryl halide bond. However, the presence of an electron-withdrawing group should also aid in the competing ionization reaction by stabilization of the phenoxide leaving group. We therefore wanted to examine substrates with the aldehyde present and the aldehyde reduced to the benzyl alcohol.

To this end, aldehyde **52** was protected as its dimethylacetal **57** by treatment with trimethyl orthoformate and catalytic *p*-toluenesulfonic acid (Scheme 11). Reduction of ester **57** with di-isobutylaluminum hydride (DIBAL-H) at −78 °C, followed by treatment of the crude alcohol with a catalytic amount of *p*-toluenesulfonic acid in aqueous methanol afforded hydroxyl aldehyde **58**. Alternatively, both the ester and the aldehyde were reduced simultaneously with DIBAl−H to furnish diol **59**.

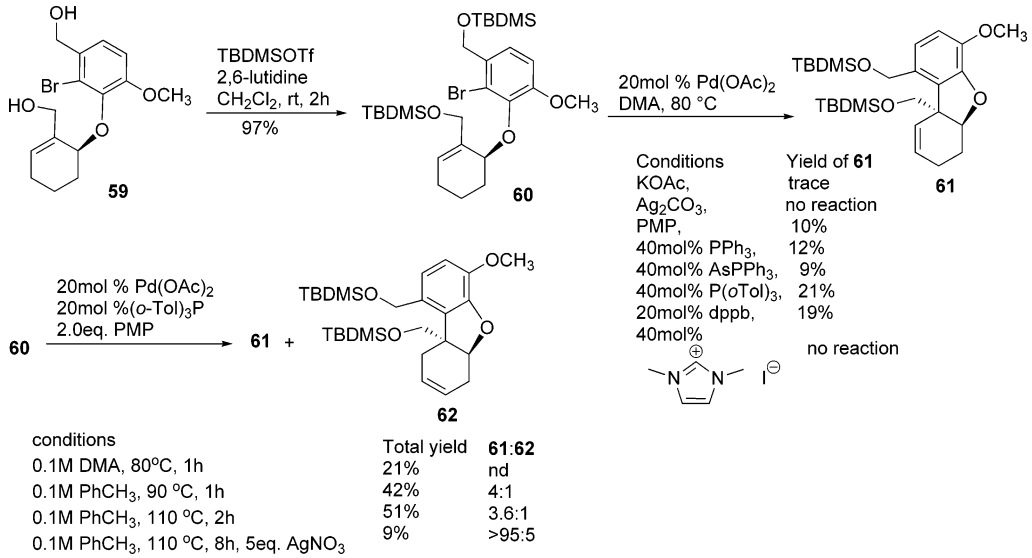
Having reduced the ester, we examined the Heck reaction of the hydroxymethyl-substituted cyclohexenes **58** and **59**. Reaction of aldehyde **58** under standard Jeffrey conditions resulted in exclusive ionization to produce phenol **26**. Attempted in situ protection of the hydroxyl group, with *N*,*O*-bis(trimethylsilylacetamide) (BSA), also resulted in rapid conversion of **58** to phenol **26**. At this point, it appeared that the presence of the electron-withdrawing aldehyde on the phenol resulted in greater acceleration of the ionization than the Heck reaction under the Jeffrey condition. Therefore, our attention turned to the Heck reaction of benzyl alcohol **59**. Unfortunately, reaction of **59**

Scheme 11. Preparation of Cyclohexenyl Alcohols for the Heck Reaction[a]



[a] Conditions: (a) $HC(OCH_3)_3$, TsOH, MeOH, 50 °C, 4 h; (b) DIBAL-H, $PhCH_3$, −78 °C, 1 h; (c) TsOH, MeOH, H_2O.

Scheme 12. Attempted Intramolecular Heck Reaction of **60**



either with use of a phosphine ligand or under Jeffrey conditions produced a complex mixture. The crude ^{1}H NMR of the reaction mixture contained aldehyde proton signals. Palladium(II) has been shown to oxidize primary alcohol producing hydridopalladium species, which in some cases have been utilized to reduce aryl halides.[119−121] The *p*-methoxy-substituted benzylic alcohol of **59** would be especially prone to oxidation by palladium.

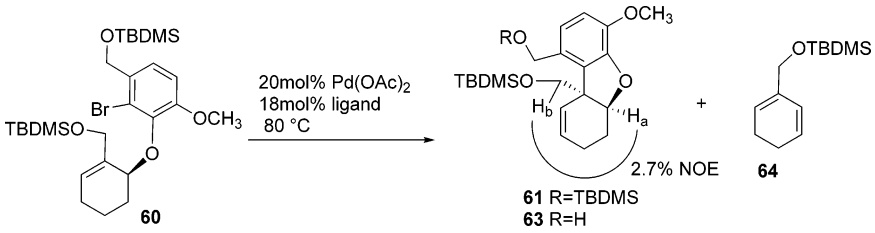
To avoid the complications caused by free alcohols, diol **59** was converted into the corresponding bis(*tert*-butyldimethylsilyl)ether **60** (Scheme 12). Reaction of arylbromide **60** under Jeffrey conditions, employing potassium acetate as base, produced only a trace of benzofuran **61**, returning mainly starting material. Changing the base to silver carbonate resulted in no reaction. Utilizing the sterically hindered amine base, pentamethylpiperidine (PMP), afforded **61 in** approximately 10% yield. Under these conditions, the major problem was catalyst lifetime (conversion) rather than the competing ionization reaction. Encouraged by these results, several ligands were investigated in order to increase turnover. Addition of triphenylphosphine or triphenylarsine to the reaction did not result in a substantial increase in the yield of benzofuran **61**. On the other hand, using tri-*o*-tolylphosphine as the ligand resulted in an increase in the yield of **61** to 21% and only a trace amount of ionization of the phenol. The bidentate ligand bis(1,4-diphenylphosphino)butane (dppb) produced a similar increase in yield (22%); however, some ionization of the phenol was still observed.

The chemoselectivity observed for the Heck reaction, over the ionization reaction, using tri-*o*-tolylphosphine as ligand prompted us to further investigate this reaction. It is presumably the steric hindrance imposed by the *o*-methyl group which inhibits coordination of the palladium(0) complex to the trisubstituted olefin of **60**, thereby preventing ionization. On the other hand, the steric requirements for the oxidative additions of the same complex to the arylbormide appear to be less stringent. Changing the solvent from dimethylacetamide (DMA) to toluene increases the yield of the benzofuran to 42% at 90 °C and 51% at 110 °C without a detectable amount of ionization. Unfortunately, significant amounts of olefin isomerization occurred and the benzofuran was isolated as a 3.6−4 to 1 mixture of the desired product **61** to the isomerization product **62**. Carrying out the Heck reaction in the presence of 5 equiv of silver nitrate suppressed the olefin isomerization; however, a drastic drop in yield was also observed. Although employing tri-*o*-tolylphosphine in the Heck reaction of **60** completely prevented ionization of the phenol, its failure to suppress both the olefin isomerization and obtain good yields of **61** led us to abandon its use.

The failure of tri-*o*-tolylphosphine as a ligand led us to more closely examine employing bidentate ligands in the Heck reaction (Table 3). Use of dppb in acetonitrile resulted mainly in phenol ionization, producing mainly diene **64** (entry 1, Table 3). Changing the solvent from acetonitrile to DMA improved the yield of **61** to 19%, while significantly decreasing the amount of ionization (entry 2). Increasing the equivalents of penta-

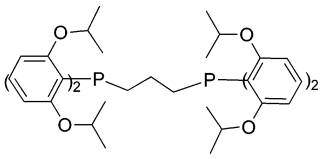
(119) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.
(120) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, 1401.
(121) Ben-David, Y.; Gozin, M.; Portnoy, M.; Milstein, D. *J. Mol. Catal.* **1992**, *73*, 173.

Table 3. Intramolecular Heck Reactions with Bidentate Phosphine Ligands



entry	ligand	conditions	yield (%) 60	61	63	64
1	dppb	0.1 M CH_3CN, 1.2 equiv of PMP, 2 h	0	8		70
2	dppb	0.1 M DMA, 1.2 equiv of PMP, 3 h	16	19		44
3	dppb	0.1 M DMA, 2.0 equiv of PMP, 2 h	32	22		33
4	dppb	0.1 M $PhCH_3$, 2.0 equiv of PMP, 2 h	32	7		51
5	dppb	0.1 M dioxane, 2.0 equiv of PMP, 10 h	32	14		33
6	dppe	0.1 M DMA, 2.0 equiv of PMP, 8 h	38	20		29
7	dppf	0.1 M DMA, 2.0 equiv of PMP, 2 h	27	7		27
8	BINAP	0.1 M DMA, 2.0 equiv of PMP, 2 h	27	17		35
9	DIP-dppp[a]	0.1 M DMA, 2.0 equiv of PMP, 2 h	24	17		58
10	dcpe	0.1 M DMA, 2.0 equiv of PMP, 12 h	5	42		25
11	dcpe	0.1 M DMA, 3.0 equiv of proton sponge, 12 h	7	50	19	0
12	dcpp	0.2 M DMA, 3.0 equiv of proton sponge, 12 h	23	33	23	0

DIP-dppp=



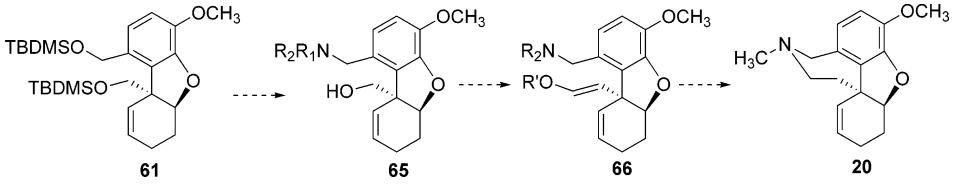
methylpiperidine (PMP) from 1.2 to 2.0 further improved the ratio of benzofuran **61** to ionization (entry 3). Employing toluene (entry 4) or dioxane (entry 5) as solvent had a dentrimetnal effect on the course of the Heck reaction. Milstein has observed that the rate of oxidative addition of palladium(0) to aryl chlorides is increased with decreasing ligand bite angles.[122,123] Changing the ligand from dppb (bite angle = 97°) to bidentate ligands with smaller bite angles, such as 1,2-bis(dipehnylphosphino)-ethane (dppe, 85°) or 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 92°) did not significantly alter the ratio of ionization to Heck reaction (entries 6 and 8). Furthermore, 1,1′-bis(diphenylphosphino)ferrocene (dppf, 95°) was less effective as a ligand (entry 7). Although decreasing the bite angle of the ligand may increase the rate of oxidative addition, this change appears not to have much effect of the relative rates of oxidative addition and the competing ionization.

It is important to note that, in all cases in which bidentate ligands were employed, less than 5% of the isomerized olefin **62** was observed. The bidentate ligands did not suppress the ionization reaction, but the sterically demanding *o*-tolylphosphine ligand did. These results led us to hypothesize that sterically demanding bidentate phosphine ligands would suppress both the olefin isomerization reaction and the phenol ionization reaction. Furthermore, sterically hindered phosphine ligands also appear to accelerate the rate of oxidative additions into aryl halides.[124−126] The di-ortho-substituted phosphine ligand, 1,3-bis[di(2,6-diisopropoxyphenyl)phosphine]propane (DIP-dppp), however, did not have the expected beneficial effect on the reaction (entry 9). We thus turned our attention to bidentate alkylphosphine ligands. 1,2-(Dicyclohexylphosphino)-ethane (dcpe) proved to be an excellent ligand for the intramolecular Heck reaction, affording benzofuran **61** in 42% yield accompanied by 25% of the ionization product **64** (entry 10). Changing the base from PMP to proton sponge further improved the reaction, furnishing **61** in 50% yield along with 19% of the monodeprotected product **63** (entry 11). More importantly, none of diene **64** derived from ionization was observed. Using a ligand with a slightly increased bite angle relative to dcpe, 1,3-(dicyclohexylphosphino)propane (dcpp), slightly decreased the catalyst turnover, but the reaction remained chemoselective for the Heck reaction over ionization (entry 12). The relative stereochemistry of benzofuran **61** was assigned on the basis of an NOE experiment.

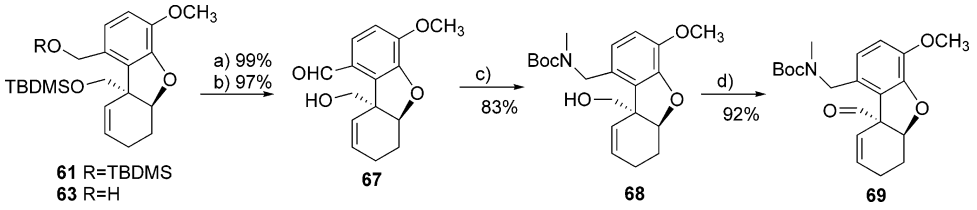
The selectivity observed for the Heck reaction over ionization in the presence of cyclohexylphosphine ligands may derive from a combination of factors. First, alkylphosphines are more electron-rich than their aryl counterparts. This has been shown to increase the rate of oxidative addition of palladium(0) to aryl halides. Conversely, electron-rich ligands should decrease the rate of the first step in the catalytic cycle of the ionization reaction, the coordination of palladium(0) to the trisubstituted olefin of **61**. Second, the steric hindrance of the dicyclohexylphosphine ligands is significantly greater than the corresponding diaryl phosphine ligands. This factor should also decrease the rate of coordination of a trisubstituted olefin. This is consistent with the selectivity observed when tri-*o*-tolylphosphine was used as ligand. This combination of electronic and steric factors present in the dicyclohexylphosphine ligand is presumably responsible for the sharp increase in relative rate of the Heck reaction to the ionization reaction.

(122) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.
(123) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655.
(124) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(125) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.
(126) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.

Scheme 13. Construction of the Galanthamine's Benzoazepine Ring

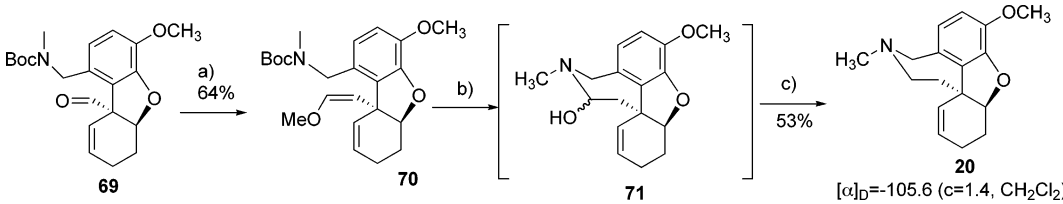


Scheme 14. Preparation of Amino-Aldehyde **69** by Reductive Amination[a]



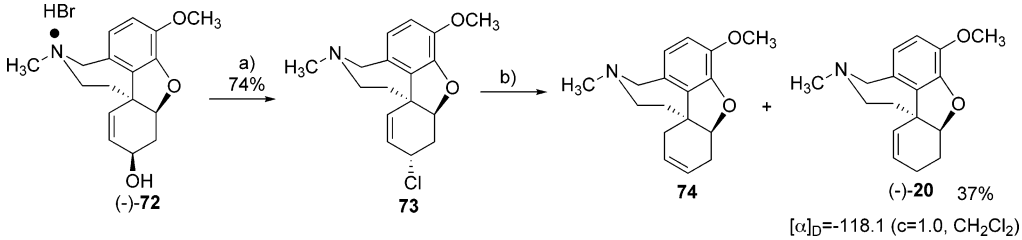
[a] Conditions: (a) TBAF; (b) MnO_2,; (c) (i) $MeNH_2$ HCl, MeOH; (ii) $NaCNBH_3$, (iii) Boc_2O, Et_3N; (d) Dess−Martin periodane, CH_2Cl_2.

Scheme 15. Formation of the Hydrobenzoazepine Ring[a]



[a] Conditions: (a) $MeOCH_2PPh_3$ Br, NaHMDS, THF, 0 °C, *Z*:*E* = 10:1; (b) TFA, CH_2Cl_2, rt, (c) (i) 4 Å MS, MeOH, 60 °C; (ii) $NaCNBH_3$, MeOH, 0 °C.

Scheme 16. Synthesis of (−)-Deoxygalanthamine from (−)-Galanthamine Hydrobromide[a]



[a] Conditions: (a) MsCl, pyr, CH_2Cl_2; (b) $LiEt_3BH$, THF, 40 °C, **20**:**74** = 3:1.

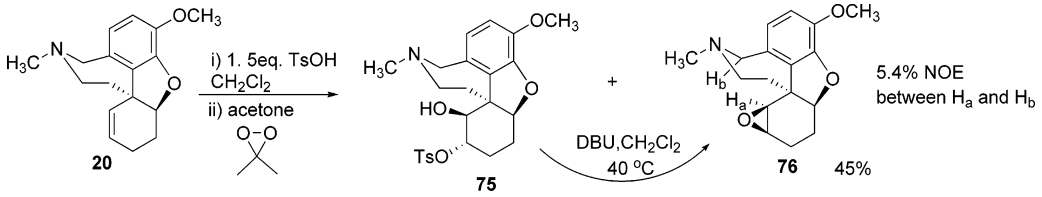
Having constructed galanthamine's benzofuran ring, we turned our attention to the preparation of the hydrobenzoazepine. We envisioned that the benzylic alcohol could be selectively oxidized and converted into amino alcohol **65** by a reductive amination (Scheme 13). We anticipated that the required one-carbon homologation could be achieved by oxidation of the alcohol to the aldehyde followed by Wittig reaction. The hydrobenzoazeping would then be prepared by hydrolysis of enol ether **66** by reductive amination.

To prepare the required alcohol **65**, the mixture of bis-**61** and monosilyl ether **63** obtained from the Heck reaction was deprotected with tetrabutylammonium fluoride (TBAF) (Scheme 14). Chemoselective manganese dioxide oxidation of the resulting benzyl alcohol afforded aldehyde **67**. Reductive amination of aldehyde **67** was accomplished by formation of the imine with methylamine followed by reduction with sodium cyanoborohydride. The resulting secondary amine was protected without isolation to supply *tert*-butyl carbamate **68**. It was necessary to protect the secondary amine because all attempts to chemoselectively oxidize the alcohol in the presence of unprotected amine resulted mainly in oxidation of the amine and recovery of aldehyde **67**. On the other hand, protected amine **68** underwent smooth oxidation, with Dess−Martin periodiane, providing aldehyde **69** in 93% yield.

The necessary one-carbon homologation of aldehyde **69** was achieved by a Wittig olefination of the aldehyde with the ylide derived from methoxymethyltriphenylphosphonium bromide and NaHMDS, producing **70** in 64% yield as a 10:1 mixture of olefin isomers (Scheme 15). Concomitant deblocking of the secondary amine and hydrolysis of the methoxyvinyl group gave a seven-membered ring hemiaminal **71** which was not isolated but immediately treated with sodium cyanoborohydride to afford (−)-3-deoxygalanthamine **20** in 53% overall yield.

The absolute stereochemistry of our synthetic 3-deoxygalanthamine **20** was confirmed by the deoxygenation of natural galanthamine hydrobromide (−)-**72** (Scheme 16). This was accomplished by first converting galanthamine hydrobromide **72** into the known chloride **73**[9] by treatment with methanesulfonyl chloride. Dehalogenation of **73** was effected by reaction with lithium triethylborohydride (Super-Hydride), which afforded a 3:1 mixture of regioisomeric olefin (−)-**20** and (−)-**74**. Comparison of the rotation of our synthetic (−)-**20** (Scheme 15) with that of (−)-**20** prepared from galanthamine (Scheme 16) confirms the absolute stereochemistry. Furthermore the

Scheme 17. Epoxidation of (−)-Deoxygalanthamine with Dimethyldioxirane

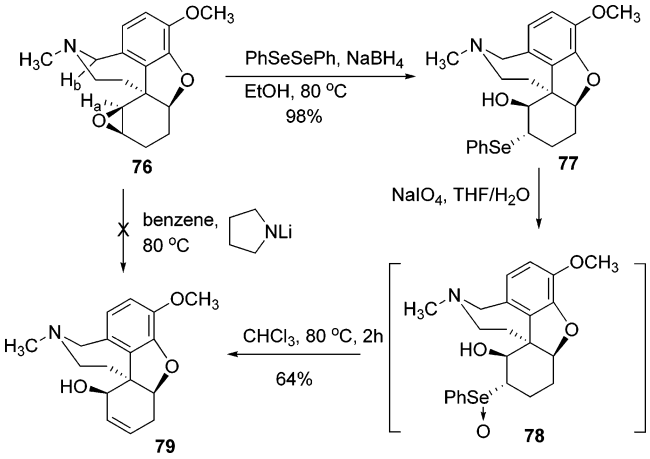


enantiomeric excess of our (−)-**20** can be calculated to be approximately 89%, indicating no deterioration of the enantiomeric excess (88%) initially achieved in the palladium-catalyzed AAA.

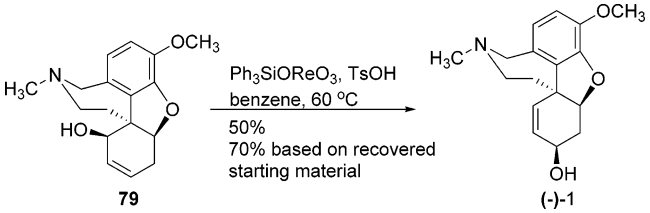
At this point, all that remained was the installation of the C3 hydroxyl group. The most direct way to accomplish this is using an allylic oxidation. We were confident this oxidation could be achieved by a method similar to that reported by Muxfeldt and co-workers in their synthesis of related *amarylidaceae* alkaloid, crinine.[101] Unfortunately, direct oxidation of 3-deoxygalanthamine **20** (SeO_2 or *tert*-butylperbenzoate, CuBr, etc.; Scheme 17) gave a complex mixture. Similar difficulties with direct allylic oxidations of alkaloids have been previously reported. Torssell and co-workers reported that all attempts to effect the allylic oxidation of deoxylycorine, using reagents such as *N*-bromosuccinimde, lead(IV) acetate, chromium(VI) oxide, and selenium dioxide, failed.[127] Instead a three-step protocol, epoxidation, phenylselenide opening−selenoxide elimination, and allylic rearrangement, was used to install the desired allylic oxygen.[127] Treatment of the ammonium salt derived from **20** and 5 equiv of *p*-toluenesulfonic aicd with dimethyldioxirane afforded a 1:1 mixture of tosylate **75** and epoxide **76**. Formation of the tosylate could be avoided by lowering the amount of *p*-toluenesulfonic acid used; however, this resulted in lower yields of **76** presumably as a result of competing formation of the *N*-oxide. Furthermore, treatment of the crude mixture of tosylate **75** and **76** with DBU cleanly converted the hydroxyl tosylate into the desired epoxide **76**. The relative stereochemistry of **76** was assigned by an NOE experiment. Irradiation of the epoxide proton (H_a, 3.20 ppm) showed a 5.4% enhancement of one of the benzylic protons (4.10 ppm). Based on the minimized structure, the epoxidation was assigned as having occurred on the olefin face anti to the hydrobenzazepine ring. It would appear that steric factors, rather than a hydrogen bond to the ammonium, are responsible for the facial selectivity of the epoxidation.[128,129]

All attempts to utilize the lithium pyrolidide to convert epoxide **76** into allylic alcohol **79** failed, returning epoxide even in refluxing benzene (Scheme 18). On the other hand, the phenylselenide opening of epoxide **76** proceeded smoothly, furnishing hydroxyselenide **77** in 98% yield. As expected, selenide attack occurred with complete selectivity for attack at the stereoelectonic favored carbon rather than the *neo*-pentyl carbon. The regioselectivity of attack was established by an ^{1}H-COSY experiment. Sodium periodate oxidation of selendie **77** produced a 1:1 mixture of diastereomeric selenoxides **78**, which surprisingly did not eliminate at room temperature. Heating of

Scheme 18. Conversion of Epoxide **76** into (−)-Isogalanthamine **79**



Scheme 19. Rhenium-Mediated Allylic Rearrangement To Produce (−)-Galanthamine



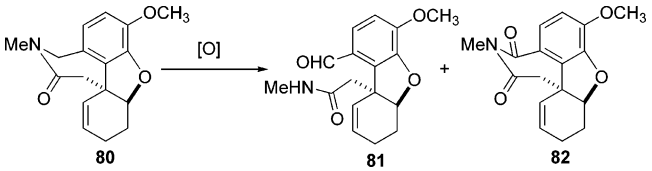
the mixture of selenoxide to 80 °C rapidly effected the elimination of one diastereomer (as observed by ^{1}H NMR), while the other diastereomer required 2 h for complete elimination. Under these conditions, (−)-isogalanthamine **79** could be prepared in 64% yield.

We investigated the use of Osborne's trioxorhenium(IV) catalyst[130] for the isomerization of isogalanthamine **79** to galanthamine (−)-**1** (Scheme 19). Under catalytic conditions only trace of amounts of galanthamine were observed in both refluxing chloroform and benzene. However, treatment of **79** first with *p*-toluenesulfonic acid followed by stoichiometric amounts of the rhenium(VII) complex afforded a 3:1 mixture of **1** and **79**. Alcohols **79** and **1** were readily separated, affording galanthamine **1** in 50% yield from **79**. The ^{1}H NMR and ^{13}C NMR of synthetic **1** are identical to those obtained from a sample of natural galanthamine. The optical rotation ($[\alpha]_D = -112.8$ ($c = 0.5$, EOH); lit.[9] $[\alpha]_D = -131.4$ ($c = 0.6$, EOH) is in accordance with those reported in the literature.

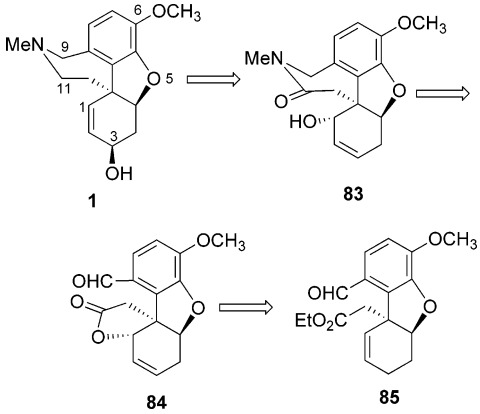
This is the first synthesis of any member of the galanthamine alkaloids in which the enantioselectivity is generated by a catalytic asymmetric reaction. All the rest of the stereochemistry was derived from the stereogenic center of chiral ether **52**. This synthesis also constitutes a formal enantioselective synthesis

(127) Moller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand., Ser. B* **1976**, *32*, 98.
(128) Asensio, G.; Mello, R.; Boix-Bernardini, C.; Gonzalez-Nunez, M. E.; Castellano, G. *J. Org. Chem.* **1995**, *60*, 3692.
(129) Asensio, G. B.-B., C.; Andreu, C.; Gonzalez-Nunez, M. E.; Mello, R.; Edwards, J. O.; Carpenter, G. B. *J. Org. Chem.* **1999**, *64*, 4705.
(130) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549.

Scheme 20. Parsons' Attempts for the Synthesis of (±)-Galanthamine[35]



Scheme 21. Synthesis of Galanthamine via Iodolactonization Strategy



of related *amaryllidaceae* alkaloids, narwedine **2** and lycoramine **3**, via oxidation or reduction.[131]

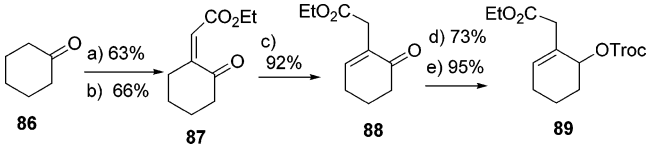
Second Generation Synthesis of (−)-Galanthamine

We can access the core structure of galanthamine, compounds **61** and **63** (Table 3), very efficiently via a sequential palladium-catalyzed AAA reaction and intramolecular Heck reaction. However, rather lengthy manipulations are required for the synthesis of the azepine ring from compounds **61** and **63** to 3-deoxygalanthamine **20**. Multiple steps are involved for the introduction of the 3-hydroxyl group (**20** to **1**). We decided to pursue a second-generation synthesis, which had three goals: (1) realization of an effective general strategy for this family of alkaloids by total synthesis of galanthamine; (2) development of a flexible strategy to provide ready access to galanthamine analogues (i.e. compound **4**) by simple modification of the synthetic scheme; and (3) development of a divergent strategy to access both *amaryllidaceae* and opium alkaloids.

During the course our investigation, two groups[34,35] independently reported the synthesis of (±)-3-deoxygalanthamine. Both groups used the same allylic alkylation (involving Mitsunobu reaction) followed by Heck cyclization strategy as our previous galanthamine synthesis. They all failed to complete the synthesis because of the difficulty of introducing the allylic hydroxyl group. Parson and co-workers tried various conditions for the allylic oxidation of lactam **80.** They did not observe any corresponding allylic oxidation product. Instead, a mixture of recovered starting material, ring cleaved product **81**, and imide **82** were obtained (Scheme 20).[35] It clearly showed that the benzylic hydrogens are much more labile toward oxidation than the allylic hydrogens.

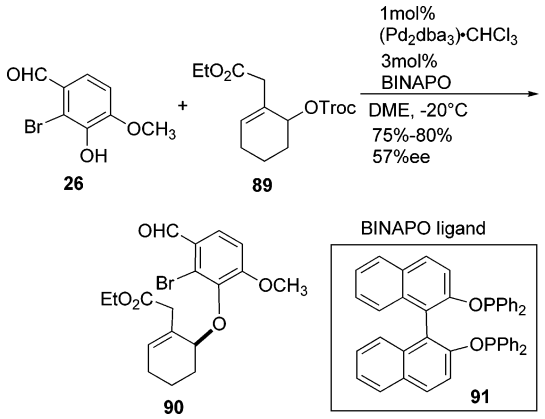
Due to the difficulty of the direct allylic oxidation, we envisioned an iodolactonization strategy to introduce the allylic OH (Scheme 21). An S_N2'-type inversion was proposed to convert 1-OH(α) to 3-OH(β).[132−134] Reductive amination of **84** followed by cyclization was proposed to synthesize the lactam

Scheme 22. Preparation of Carbonate **89**[a]



[a] Conditions: (a) $CHOCO_2Et$, Dabco/toluene; (b) $MsCl/Et_3N$/DMAP; (c) DBU/cyclohexane, reflux; (d) $NaBH_4$, $CeCl_3$; (e) $Cl_3CCH_2OC(O)Cl$, pyr.

Scheme 23. Palladium-Catalyzed AAA of **26** and **89**



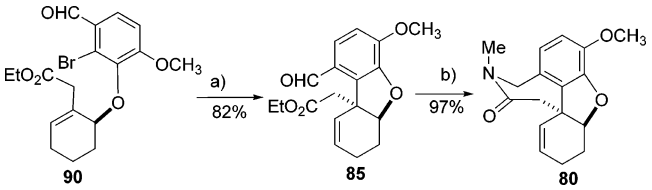
ring of **83**. Compound **85,** which is readily available from Pd-catalyzed AAA followed by Heck cyclization, can be converted to lactone **84** by iodolactonization promoted by either iodine or NIS followed by base-mediated elimination.

The synthesis begins with the preparation of carbonate **89** (Scheme 22). Compound **88** had been prepared from a tandem Birch reduction of methyl 2-methoxybenzoate followed by alkylation with ethyl 2-bromoacetate and hydrolysis.[103] We found that a three-step protocol in Scheme 22 is more suitable for large-scale preparation of known enone **88**.[135] Luche[104] reduction followed by acylation provided carbonate **89**.

Various conditions failed to catalyze the allylic alkylation of phenol **26** with carbonate **89** using ligands **42** and **53**−**55** (Table 2) and other ligands in our hands. BINAPO ligand **91**, the first chiral ligand developed for the palladium-catalyzed AAA reaction in this group,[136] is the only ligand that worked for the reaction among all ligands we examined (Scheme 23).[137] Aryl ether **90** can be obtained in high yield (75−80%) but only moderate enantioselectivity (57%ee) in the presence of BINAPO ligand under various conditions. The absolute stereochemistry of compound **90** is not determined due to the low enantiomeric excess.

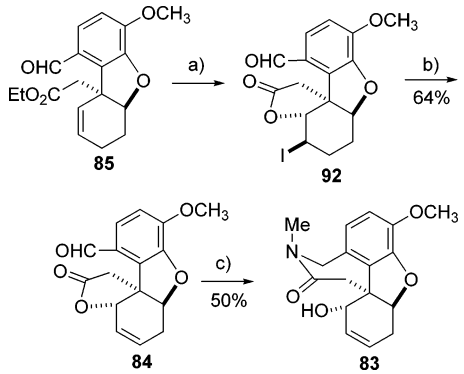
To test the validity of the proposed synthetic plan (Scheme 21), aryl ether **90** was cyclized to give **85** in the presence of $Pd(OAc)_2$/dppp and excess silver carbonate (Scheme 24).[34,35] Significant amounts of olefin isomers were found when potassium carbonate was used as base or less silver carbonate was employed. Early results[118] and results from our previous synthesis of galanthamine suggested that the presence of electron-withdrawing substituents on the phenol ring favored the palladium-catalyzed ionization over the intramolecular Heck reaction. The success of current reaction suggests that the electron-withdrawing group on the olefin favored the ionization, while the electron-withdrawing group on the phenol ring facilitated oxidative addition of the palladium to both the C−O and C−Br bonds. The relative stereochemistry of benzofuran

Scheme 24. Intramolecular Heck Reaction and Cyclization of the Benzoazepine Ring[a]



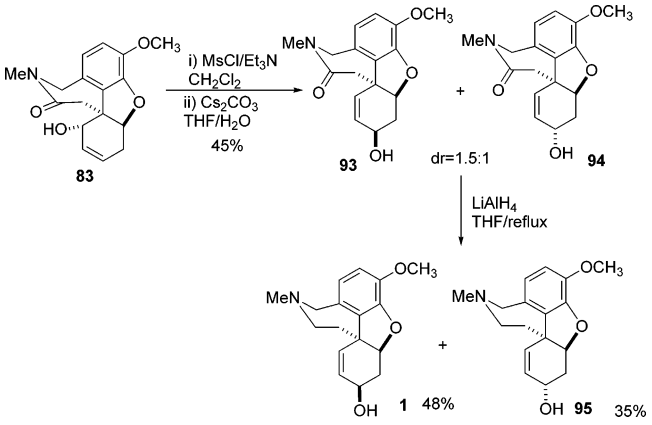
[a] Conditions: (a) 15 mol % Pd(OAc), 15 mol % dppp, $PhCH_3$, 3 equiv of Ag_2CO_3; (b) $MeNH_2$/MeOH, $NaBH_4$, 0 °C.

Scheme 25. Iodolactonization and Cyclization of the Hydrobenzoazazepine Ring[a]



[a] Conditions: (a) (i) 1 N NaOH, MeOH then 3 N HCl; (ii) NIS, DMAP, MeCN; (b) DBU/THF; (c) $MeNH_2$/MeOH, then $NaBH_4$.

Scheme 26. Synthesis of Galanthamine and 3-*epi*-Galanthamine

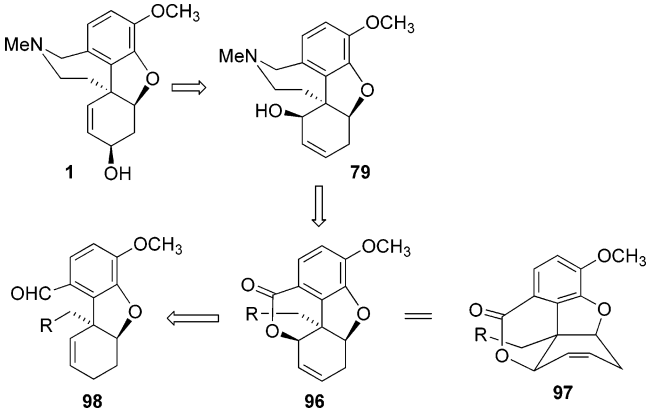


85 was assigned on the basis of analogy to Heck cyclization of compound **60** (Table 3). Reductive amination of **85** provided lactam **80** in high yield. Attempts for the allylic oxidation of lactam **80** were not successful, which has been observed by Parsons[35] as well (Scheme 20).

Direct iodolactonization of **85** was not successful. A one-pot hydrolysis, iodolactonization followed elimination procedure provided lactone **84** in 64% overall yield (Scheme 25). Reductive amination and amidation were achieved in a single operation, giving lactam **83** in 50% yield.

The allylic alcohol **83** was activated and subjected to basic hydrolysis (Scheme 26).[132−134] Two isomers (**93** and **94**) in a ratio of 1.5:1 were obtained without any recovery of the starting material on the basis of crude ^{1}H NMR. Both isomers were collected and reduced by $LiAlH_4$ in refluxing tetrahydrofuran (THF). By comparing the ^{1}HNMR of known galanthamine **1**[32] and 3-*epi*-galanthamine **95**,[25,75] the major isomer (isolated in 48%) was identified as natural galanthamine **1**, and the minor isomer (isolated in 35%) was assigned as 3-*epi*-galanthamine **95**.

Scheme 27. Alternative Iodolactonization Strategy



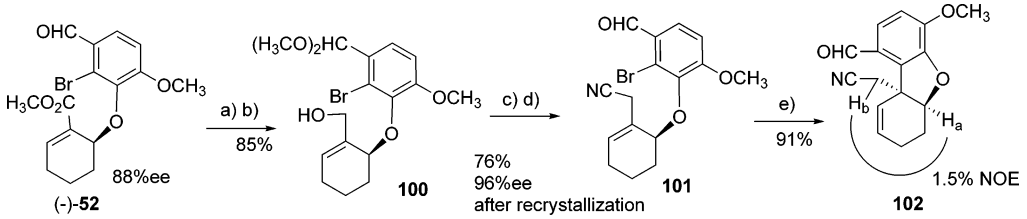
Third Generation Synthesis of (−)-Galanthamine and Its Analogue

The low overall efficiency and selectivity of the above strategy prompted us to pursue a new strategy to introduce the allylic hydroxyl group. We decided to take the advantage of the known 1,3-rearrangement of penultimate precursor **79** to galanthamine **1 (**Scheme 19) in our first generation synthesis of galanthamine. We envisioned a new oxidation−iodolactonization−elimination sequence to introduce the allylic oxygen of compound **96** directly from compound **98** (Scheme 27). Conformation analysis showed that the carboxylic acid derived from oxidation of aldehyde **98** could only access the more hindered β-face of the olefin intramolecularly to give lactone **96** (as depicted in conformation **97**).

Compound **98** can be prepared either directly from aryl ether **90** (Scheme 23) via Heck cyclization or from aryl ether **52** (Table 2) with some functional group manipulations followed by Heck cyclization. Due to the difficulty in achieving good enantioselectivity of ether **90**, we decided to prepare compound **98** from aryl ether **52**, which can be obtained with high optical purity (88%ee) using palladium-catalyzed AAA reaction (Table 2). On the basis of the success of the Heck reaction for substrate **90** (Scheme 24), we decided to keep the aldehyde functionality of ether **52** while removing the electron-withdrawing substituent on the olefin by homologation of the α,β-unsaturated ester to a α,β-unsaturated nitrile (Scheme 28). To this end, aldehyde **52** was protected as its dimethylacetal by treatment with trimethyl orthofomate and catalytic *p*-toluenesulfonic acid. It would be more convergent if the acetal can be formed before the AAA reaction. Neither methanol nor ethylene glycol can produce pure acetal. The acetal obtained was quickly hydrolyzed when exposed to air. Selective reduction of the α,β-unsaturated ester with diisobutylaluminum hydride (Dibal-H) at −78 °C afforded allylic alcohol **100**. The α,β-unsaturated nitrile **101** was prepared

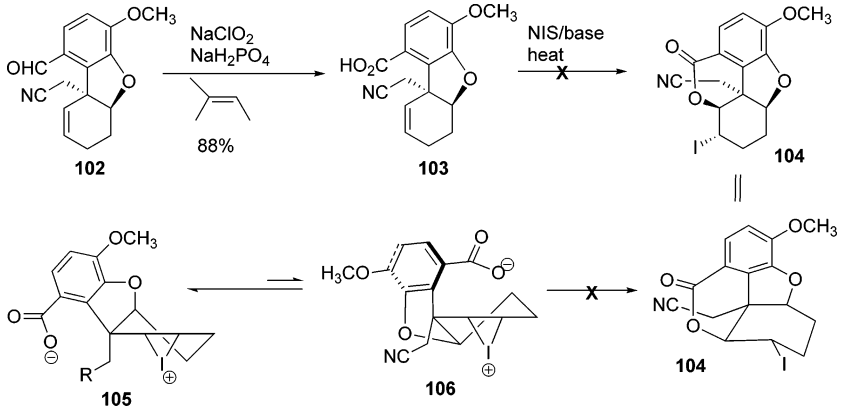
(131) Lee, T. B. K.; Goehring, K. E.; Ma, Z. *J. Org. Chem.* **1998**, *63*, 4535.
(132) Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294.
(133) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2529.
(134) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.
(135) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181.
(136) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(137) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263.

Scheme 28. Synthesis of Compound **102**[a]



[a] Conditions: (a) 1.5 mol % TsOH, $CH(OMe)_3$, MeOH; (b) 2. DIBAL-H/Tol, −78 °C; (c) 1. Ph_3P, acetonecyanohydrin, DIAD, Et_2O; (d) 2.20 mol % TsOH, THF, H_2O; (e) 15 mol % $Pd(OAc)_2$, 15 mol % dppp, 3 equiv of Ag_2CO_3, $PhCH_3$, 107 °C.

Scheme 29. Attempted Iodolactonization of Acid **103**



in 84% yield using a modified Mitsunobu protocol[138,139] followed by acid hydrolysis. The enantiomeric excess of **101** was improved to 96% by recrystallization from diethyl ether and petroleum ether with 90% mass recovery. We then examined the Heck reaction of the acetonitrile-substituted cyclohexene **101**. High yield (91%) of the Heck product **102** was obtained using a catalytic amount of diphenylphosphinopropane (dppp) and $Pd(OAc)_2$ in refluxing toluene in the presence of excess of silver carbonate, conditions similar to the cyclization of **90** (Scheme 24).[34,35] Other solvent (DMF) or ligands (dppe, dppf) gave lower yield. Lower conversion and olefin isomerization were observed with lower catalyst loading or less amount of silver carbonate.

Aldehyde **102** was oxidized to acid **103** uneventfully (Scheme 29). All attempts for the iodolactonization of acid **103** under the same condition for acid derived from ester **85** (Scheme 25) or more forcing conditions (high temperature) failed, and most of the starting materials were recovered. In the case of acid derived from ester **85** the electrophile (NIS) approached the olefin from the more hindered β-face (syn to the bulky aryl group). Formation of iodonium species **105** should be a facile process since the electrophile (NIS) now approaches the olefin from the less hindered α-face (anti to the bulky aryl group). However, to bring the carboxylic acid in close proximity to the olefin, the cyclohexene ring has to adopt the less stable conformation **106**, where the bulky aromatic ring is on the pseudoaxial position. Furthermore, the diaxial trajectory required for the attack of the carboxylate to iodonium ion cannot be fulfilled in conformation **106**.

There are primarily two reasons for the failure of the direct allylic oxidation of deoxygalanthamine **20** (Scheme 16) in our first generation synthesis, the competitive oxidation of the tertiary amine and the benzylic protons (Scheme 20).[34,35] We decided to reexamine the allylic oxidation strategy on substrate **102**, where the benzylic position is protected as the aldehyde and the tertiary amine is masked as nitrile. This can be realized by oxidation of the olefin to an enone followed by known diastereoselective 1,2-reduction or, more efficiently, direct oxidation to the allylic alcohol, which raises the question regarding the diastereoselectivity. Usually, the electrophile would approach the olefin from the less hindered convex face. We envisioned that SeO_2 would react with the olefin from the more hindered concave face through an ene mechanism[140] (structure **108**, Scheme 30), because the axial proton H_{ax} is perfectly aligned with the π system. Gratifyingly, treatment of olefin **102** with SeO_2 in dioxane at 150 °C in a sealed tube provided alcohol **107** in 57% yield (dr = 10:1) with 7% recovered starting material in the presence of NaH_2PO_4 and quartz sand.[141] Other additives, such as HCO_2H,[142] $InCl_3$, $YbCl_3$, and Na_2HPO_4, gave less of the desired product. Attempts to fully convert all the starting material by extending the reaction time or increasing the temperature resulted in more decomposition. Only a trace amount of product was found in refluxing dioxane (110 °C) after 8 h. This represents the first successful allylic oxidation[32,35] of the galanthamine skeleton. The stereochemistry of **107** was tentatively assigned on the basis of coupling constants of H_a/H_{eq} and H_b/H_{eq} ($J < 5.0$ Hz). The high diastereoselectivity reflects the stereoelectronic requirement for the ene reaction.

Compound **107** together with its epimer (dr = 10:1) was then converted to the natural product in a one-pot process (Scheme 31). Aldehyde **107** was treated with methylamine in methanol

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(139) Aesa, M. C.; Baan, G.; Novak, L.; Szantay, C. *Synth. Commun.* **1995**, *25*, 1545.
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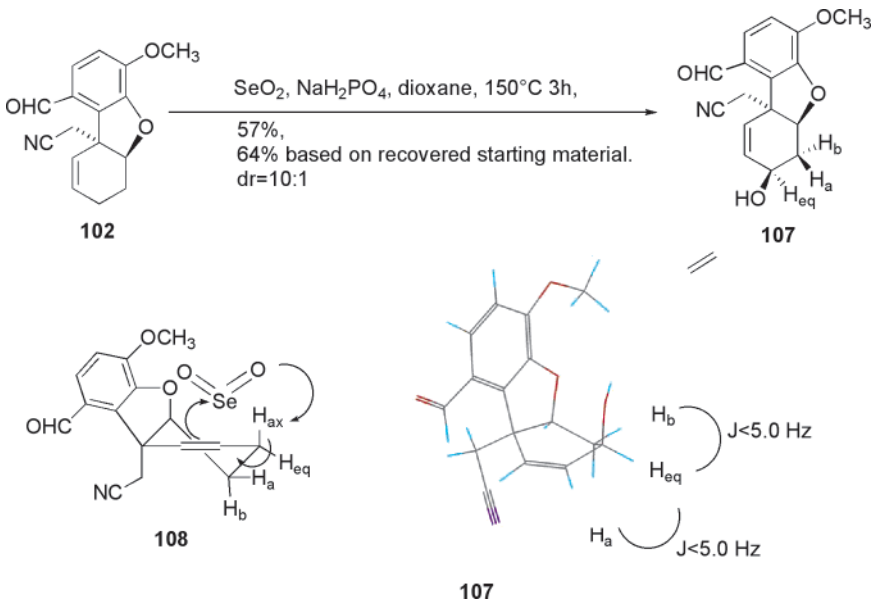
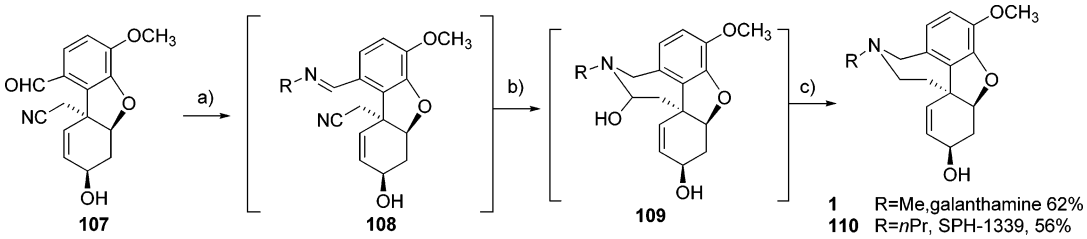
(142) Shibuya, K. *Synth. Commun.* **1994**, *24*, 2923.

Scheme 30. Direct Diastereoselective Allylic Oxidation of **102**



Scheme 31. One-Pot Completion of the Synthesis of (−)-Galanthamine and Its Derivative[a]



[a] Conditions: (a) RNH_2, MeOH; (b) 4 equiv of DIBAL-H, then aqueous NaH_2PO_4; (c) $NaCNBH_3$.

solution. Excess methylamine and methanol was removed under vacuum. Concomitant reduction of the imine and nitrile by DIBAL-H followed by acid quenching presumably gave a seven-membered ring hemi-aminal **109**. The resulting solution was directly treated with sodium cyanoborohydride to afford (−)-galanthamine **1** and 3-*epi*-galanthamine **95** (Scheme 26) in 62 and 6% isolated yields, respectively. All spectral data (^{1}H NMR, ^{13}C NMR, IR) $[\alpha]_D = -123.1$ ($c = 0.4$, EtOH), lit.[9] $[\alpha]_D = -131.4$ ($c = 0.6$, EtOH)) are identical to those of a sample of the natural product and data from previous synthesis.

Simply switching methylamine to propylamine, SPH-1339 **110**[14], a slightly more potent inhibitor of Ache compared to (−)-galanthamine **1**, was prepared in 56% yield by this one-pot process. Previous syntheses of this type of galanthamine derivatives require demethylation of galanthamine via Polonovski reaction[15] followed by alkylation of the resulting norgalanthamine.[12,14]

The third generation synthesis[33] of galanthamine (10 steps, 96% ee, 8% overall yield from commercially available glutaraldehyde **35** and isovanillin **25**) is a significant improvement over and successfully addresses many of the shortcomings of the first generation synthesis[32] (16 steps, 88% ee, 0.8% overall yield). Furthermore, switching methylamine to other alkylamines in the last step can provide easy access to various galanthamine derivatives, demonstrated by the synthesis of SPH-1339. The sequential palladium-catalyzed AAA and intramolecular Heck reaction followed by a diastereoselective allylic oxidation provided the key intermediate **107** with all the functionality installed except the hydrobenzoazepine ring. The one-pot reductive cyclization represents a simple and efficient strategy to form the latter and to access many galanthamine analogues.

Enantioselective Synthesis of (−)-Codeine and (−)-Morphine

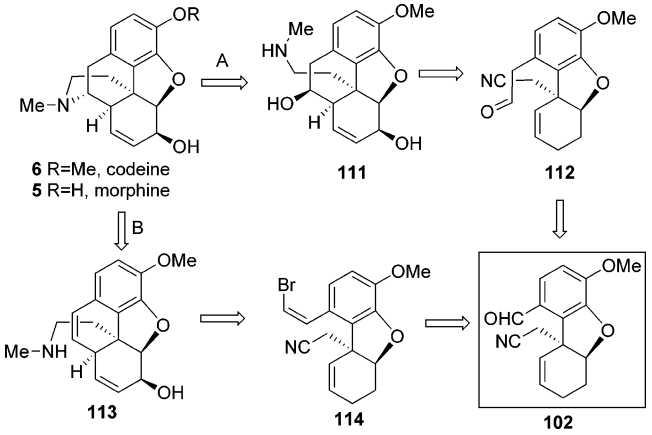
In our synthesis of galanthamine **1** and its derivative SPH1339 **110**, we established a practical synthesis of cyanoaldehyde **102** in only five steps from Pd-AAA product **52** (Scheme 28). On the basis of the diversified strategy proposed in Scheme 3, we then pursued the synthesis of opium alkaloids starting from intermediate **102**, which has the common tricyclic core of opium alkaloids and appropriate functionalized side chains (R_1 and R_2 of compound **19**, Scheme 3) that can be transformed to the additional rings of the opium alkaloids.

Scheme 32 outlines two strategies based upon formation of the piperidine ring as the final ring-forming event.[143,144] In path A, a straightforward displacement of amino alcohol **111** envisions formation of the latter via a carbonyl ene reaction of aldehyde **112**, which, in turn, may derive by homologation of cyanoaldehyde **102**. Path B outlines a more intriguing, but more speculative, strategy in which the piperidine ring would arise by a hydroamination of amine **113**, which, in turn, may derive from Heck vinylation of *Z*-vinyl bromide **114**. A simple olefination protocol should allow the latter to derive from the same aldehyde **102**.

Scheme 33 outlines the initial efforts based upon path A. Homologation of the aldehyde proceeded uneventfully via

(143) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688.
(144) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473.

Scheme 32. Retrosynthetic Analysis of Opium Alkaloids



rearrangement of an epoxide intermediate. All attempts to effect the intramolecular carbonyl ene reaction to form alcohol **115** failed.

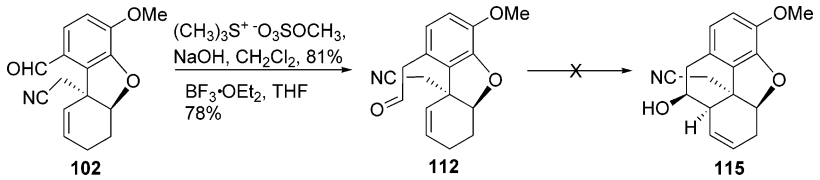
Thwarted in attempts to execute path A, we turned to path B. Olefination[145] followed by chemoselective reduction of the *E*-vinyl bromide[146] provided the cyclization substrate **114** (Scheme 34). Intramolecular Heck vinylation to the sterically congested neopentyl carbon created the tetracycle **117** in good yield under the same conditions used for the Heck reaction of compounds **90** and **102** (Scheme 24 and Scheme 28).[33]

With the skeleton of morphine in hand, our attention focused on allylic functionalization (Scheme 35). Based upon the known conformation of morphine,[147] both H_a and H_b of alkene **117** are stereoelectronically and sterically favored for allylic oxidation. Despite H_a being doubly allylic, its removal with selenium dioxide is clearly strained due to creation of the bridgehead double bond. Indeed, subjecting **117** to this reagent only involves abstraction of H_b to give the corresponding alcohol **118** accompanied by the overoxidation product ketone **119**. Directly adding the Dess–Martin periodinane to the reaction mixture prior to workup allowed ketone **119** to be isolated in 58% yield. Its reduction proceeded stereoselectively with DIBAL-H in THF–ether to give the required alcohol **120** almost quantitatively. No reduction of the nitrile was observed in this solvent system. Furthermore, none of alcohol **120** was detected in the initial allylic oxidation.

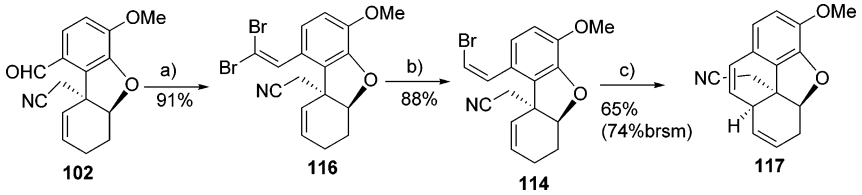
Adapting a known protocol,[148] the nitrile **120** was converted to the secondary amine **113** in a one-pot operation (Scheme 36). Switching from THF to methylene chloride allowed nitrile reduction to the imine aluminum complex. Addition of ammonium bromide in dry methanol destroyed excess DIBAL-H and freed the imine. Subsequent addition of excess methylamine converted the primary imine to the more stable secondary one (Scheme 36). The final stage involved addition of sodium borohydride wherein amine **113** was obtained quantitatively from alcohol **120**. Performing this same protocol on ketone **119** also converted it to amine **113**, thereby saving one step.

The stage was set for the closure of the final piperidine ring. Parker,[143] Mulzer,[149–151] and Ogasawara[152,153] synthesized 7,8-

Scheme 33. Attempted Carbonyl Ene Reaction

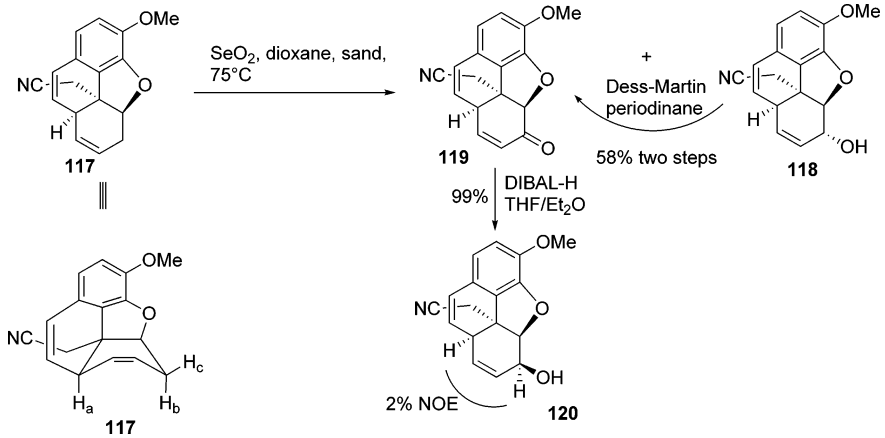


Scheme 34. Heck Cyclization of Vinyl Bromide[a]

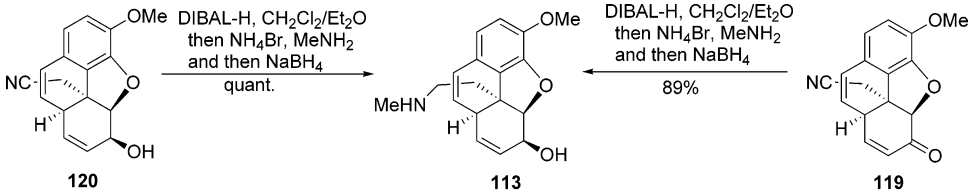


[a] Conditons: (a) CBr_4, Ph_3P, CH_2Cl_2; (b) 5 mol % $Pd(PPh_3)_4$, n-Bu_3SnH, $PhCH_3$; (c) 15% $Pd(OAc)_2$, 15% dppp, Ag_2CO_3, toluene.

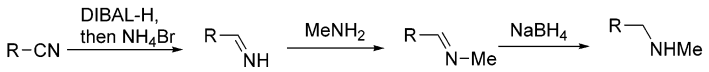
Scheme 35. Allylic Oxidation of Compound **117** and Diastereoselective Reduction



Scheme 36. Sequential Reduction−Transamination−Reduction



Mechanism of the tandem reduction-transamination-reduction

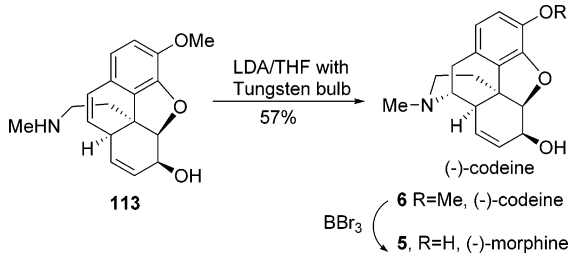


dihydrocodeinone by cyclizing the final piperidine ring via a radical anion process (Li/NH_3/*t*-BuOH) from a tosyl amide derivative. We decided to investigate the direct ring closure of secondary amine **113** to codeine via hydroamination. Carefully examining the functional group compatibility of all known olefin hydroamination reactions,[154−164] the base-catalyzed hydroamination appeared to be the most promising method for the hydroamination of amine **113**.

The first example of base-catalyzed intermolecular hydroamination of vinylarenes appeared in 1948.[165] The anti-Markovnikov addition product was obtained as the major product albeit in low yield. The hydroamination of styrene derivatives using alkyllithium as precatalyst was first reported in 1972.[166] The alkyllithium-catalyzed hydroamination of styrene has been extended to more complicated amines and more substituted vinyl aromatics by Beller [155,167,168] and other groups.[169,170]

Base-catalyzed intramolecular hydroamination of vinyl arenes was only studied for the formation of five-membered rings.[171] It has been shown that more than stoichiometric amounts of base (i.e. BuLi) give lower yields. Although monosubstituted alkenes cyclize smoothly, more substituted alkenylamines and electron-rich vinylamines (e.g. *p*-$CH_3O-C_6H_4-CH{=}CH(CH_2)_3$-$NHCH_3$) do not cyclize in the presence of either stoichiometric or catalytic amounts of *n*BuLi.[172] However, under anodic oxidative conditions,[173,174] the lithium amide of electron-rich vinylamines can cyclize to corresponding pyrrolidines in moderate yield.[172]

Scheme 37. Light Promoted Hydroamination



Simply treating **113** with various amounts of lithium diisopropylamide (LDA) or *n*-butyllithium in refluxing THF led to recovered starting material up to 2 h and extensive decomposition after 8 h. With the notion that the addition might be facilitated by single electron transfer,[172−177] promotion of the latter by irradiation of the basic solution with an ordinary tungsten light bulb[178,179] was envisioned. Indeed, subjecting the solution of amine **113** and 6 equiv of LDA in THF to such irradiation with a 150-W tungsten light bulb led to cycloisomerization to form (−)-codeine whose spectral data are identical to those previously reported (Scheme 37).[180,181] Less amount of base led to lower conversion. Demethylation as reported by Rice[182] with boron tribromide converts this route into a synthesis of (−)-morphine as well.

This very short asymmetric total synthesis of (−)-morphine (15 longest linear steps with 3.2% overall yield and 16 total steps from commercially available materials) arises because of the minimal use of protecting groups. Palladium-catalyzed reactions, AAA and two Heck-type, create the entire carbon framework and four rings. The one-pot reduction−transamination−reduction of nitriles significantly shortens the route. Most

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(162) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.
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noteworthy is the effectiveness of the intramolecular hydroamination promoted by visible light—a reaction that should prove more generally useful in alkaloid synthesis.

Conclusion

All three generations of syntheses of galanthamine and the synthesis of morphine feature the sequential palladium-catalyzed asymmetric allylic alkylation and Heck cyclization. We developed three different ways to introduce the allylic alcohol diastereoselectively. Among them, the direct allylic oxidation is the most efficient and selective one. The third generation synthesis of galanthamine is different from previous ones by closing the benzoazepine ring in the last step. This provided easy access to various galanthamine analogues demonstrated by the synthesis of SPH-1339. This is the shortest and most efficient nonbiomimetic total synthesis of (−)-galanthamine to date. (−)-Galanthamine and (−)-morphine are now available in two steps (35% yield) and seven steps (14% yield), respectively, from the common intermediate **102,** which can be prepared enantioselectively from commercial available glutaraldehyde **35** and isovanillin **25** in eight longest linear (23% overall yield) and nine total steps. Strategically, the commonality of the amaryllidaceae and opium alkaloids from a chemical synthesis perspective has now been established. All the stereochemistry emanates from the palladium-catalyzed AAA. Since both enantiomers of ligand **55** are available,[141] both galanthamine and morphine are available, as either enantiomer, from commercial available materials. This strategy should allow for entry into a variety of *amaryllidaceae* alkaloids and opium alkaloids with similar skeletons.

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Supporting Information Available: Compound spectra and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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