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Modular access to vicinally functionalized allylic (thio)morpholinonates and piperidinonates by substrate-controlled annulation of 1,3-azadienes with hexacyclic anhydrides†‡

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A modular substrate-controlled hexannulation of inherently promiscuous 1,3-azadienes with hexacyclic anhydrides, which affords versatile vicinally functionalized allylic lactams, in high yields, regio- and stereoselectivities is described.

Introduction

Functionalized piperidines, morpholines and thiomorpholines (see highlighted rings in Fig. 1) constitute the core of several alkaloid natural products, natural or unnatural amino acids, ligands and pharmaceuticals.[1]

Fittingly, the biological relevance of these N-, N,O-, and N,S-heterocycles (*e.g.*, pandoline is an *aspidosperma* alkaloid with anticancer activity[2] and viloxazine is a selective norepinephrine reuptake inhibitor[3]) as well as their architectural complexity endear them to the medicinal and synthesis communities, thus, inspiring the development of increasingly more *efficient* and *modular* strategies for their construction, functionalization, and evaluation of their structure–activity relationships. Toward this end, several elegant systematic scaffolding strategies have emerged including those employed by Bode[4,5] (using SnAP reagents), Bosch[6] (using bicyclic lactams), Comins[7–9] and Georg[10–15] (using dihydropyridones), Liebeskind[16] (using organometallic scaffolds) Aggarwal[17,18] (using α-phenylvinylsulfonium salts), Tiecco[19] (using vinyl selenones), Xia[20] (using aziridines), Carreira[21,22] (using spirocyclic 3-oxetanones), Wolfe[23] (using Pd-catalyzed intramolecular carboamination), MacMillan[24,25] (using photoredox catalysis) and Schafer[26,27] (using catalytic alkylamination/reduction).

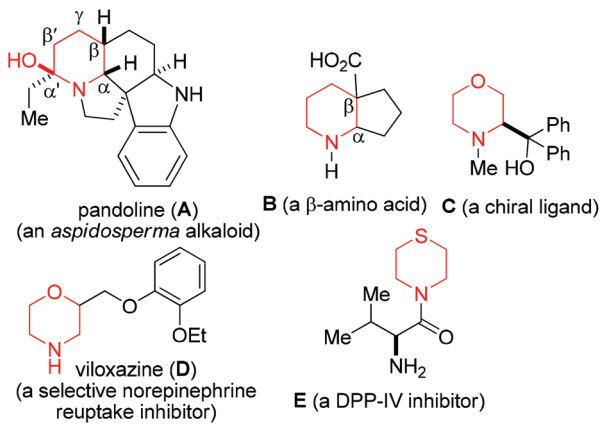

Fig. 1 Examples of bioactive azaheterocycles.

Circumscribed in these classes of azaheterocycles is a subset, which bears *vicinal stereocenters*. However, controlling the formation of (labile) vicinal stereocenters on the skeleton of a piperidine or (thio)morpholine poses a considerable challenge, in part because sequential substitution of a 2- or 3-substituted cyclic amine derivative is only marginally tolerated in most of the existing C-2 or C-3 functionalization strategies. Along these lines, we previously disclosed that the addition of alkyllithium nucleophiles to the β-position of α-arylated dehydropiperidines followed by interception of the intermediate tertiary organolithium with electrophiles furnishes polysubstituted benzylic piperidine derivatives in excellent diastereoselectivities (Fig. 2A).[28,29] Disappointingly, from the standpoint of generality, dehydromorpholines tended to undergo undesirable ring opening. Perhaps more disheartening to date is our inability to extend the methodology to α-alkenyl enecarbamates as we are caught at the crossroads of alkene *vs.* enecarbamate carbolithiation.

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† Dedication: T. K. B. dedicates this paper to the memory of his former organic chemistry instructor and department chair at the University of Buea, Professor Samuel Fanso Free. His encouragement and selfless mentorship during those incipient stages will forever be appreciated.

‡ Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c6ob01526c

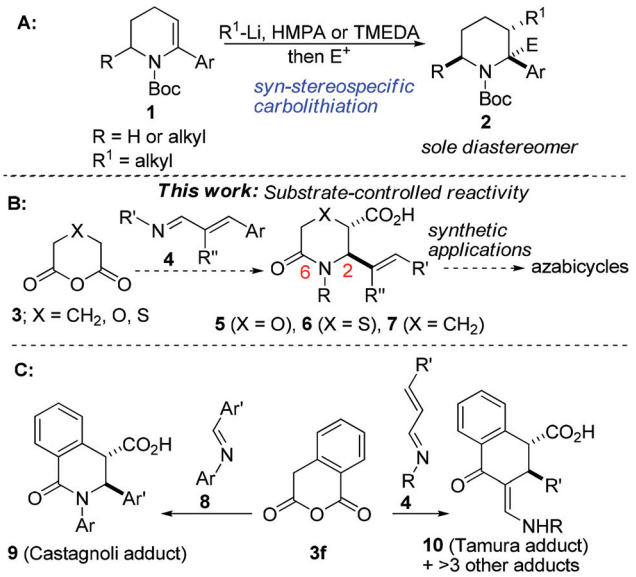


Fig. 2 (A) Vicinal functionalization of α-arylated dehydropiperidines by carbolithation-trapping[28,29] (B) proposed plan for accessing vicinally functionalized allylic morpholinones, thiomorpholinones and piperidinones (C) annulation of homophthalic anhydride with 1,3-azadienes.[30,31]

Desiring a *modular* approach to *vicinally* functionalized and potentially bioactive N-heterocycles bearing an *alkenyl motif* at the α-amino position, and seeking to side-step the aforementioned limitations, we became interested in investigating the fate of hexacyclic anhydrides of type **3** in formal [4 + 2] cycloadditions with 1,3-azadienes such as **4** (Fig. 2B, see **5**–**7**). We were fully aware of Haimova's previous findings that while homophthalic anhydride (**3f**) reacts efficiently with simple aromatic imines such as **8** to afford azaheterocyclic Castagnoli-type cycloadducts of type **9**,[30,31] its reaction with α,β-unsaturated imines such as **4** proceeds through a plethora of reaction pathways, including Tamura-like[32–34] (see carbocyclic enaminone **10**, Fig. 2C), Castagnoli-type and Perkin condensation-type[35] pathways. Indeed, the promiscuous nature of **4** has understandably led researchers to the somewhat hasty conclusion that its reaction with cyclic anhydrides is '*synthetically unattractive*'.[35] We therefore stoically embraced the challenge and surmised that the *decreased α-CH acidity* of anhydrides **3a–e** would serve to provide an ideal balance of reactivity and selectivity. We reasoned that the appendage of an alkenyl motif on the skeleton of a nitrogen heterocycle would pave the way for harnessing several reactivity modes, including hydrogenation,[36] hydroarylation,[37] oxoamination,[38] metathesis,[39] or trifluoromethylation.[40] It was however recognized that successful implementation of the planned strategy would hinge on our ability to (i) achieve *substrate-controlled reactivity*, (ii) mitigate *E*/*Z* isomerization or double-bond migration, and (iii) achieve site-selective functionalization of **5**–**7**. Herein, detailed efforts toward the elicitation of our ideals are described.

Results and discussion

We initiated studies on the construction of vicinally functionalized *allylic* lactamoyl acids/esters by assembling a diverse range of 1,3-azadienes (Fig. 3, see **4a–x**).

Foremost among our objectives was to access allylic morpholinonates. Gleaning from recent insightful reports from the laboratories of Burdzhiev[41] and Krasavin[42] on the use of digylcolic anhydride (**3b**) in a Castagnoli–Cushman reaction with unconjugated imines, model azadiene **4a** and **3b** were engaged in a thermally induced [4 + 2] cycloaddition, using toluene as the solvent. Pleasingly, after stirring for 12 h at 90 °C, GC-MS and ^{1}H NMR analyses of the methylated crude mixture revealed the presence of a single cycloadduct (Scheme 1, see **5a2**). The exclusive and stereodefined formation of *E*-configured styrene derivative **5a2** indicates a preference for a Castagnoli–Cushman-type reaction over a Tamura-like cycloaddition; the latter being the preferred pathway when homophthalic anhydride was employed (see **10**, Fig. 2C).[31] Encouraged by this outcome, and after establishing that toluene out-performs other solvents (*e.g.*, EtOAc, 2-MeTHF and 1,4-dioxane), we next moved to evaluate the scope of the transformation with respect to the *N*-substituent and the alkenyl motif. In the event, we have found that electronically diverse imino dienes are well tolerated. For example, allylic lactam **5c2**, which bears an electron-donating *p*-methoxy-

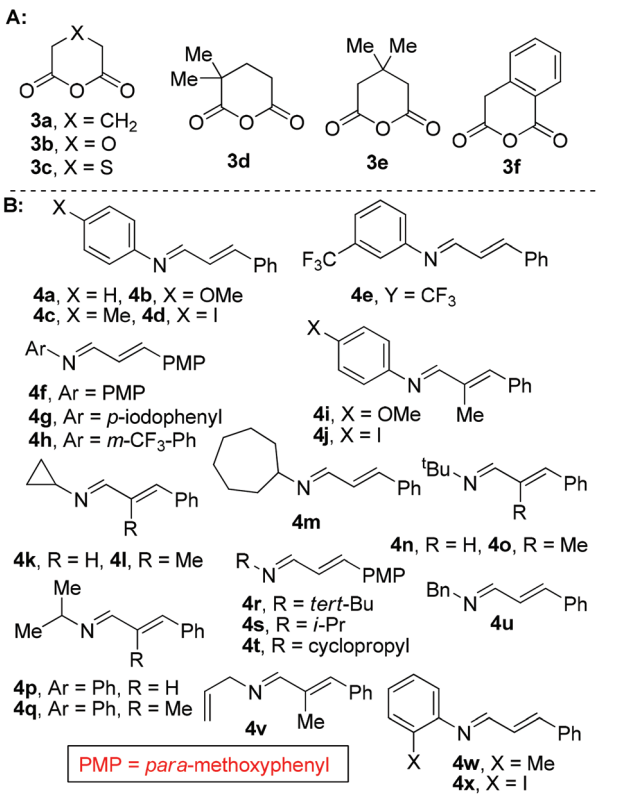
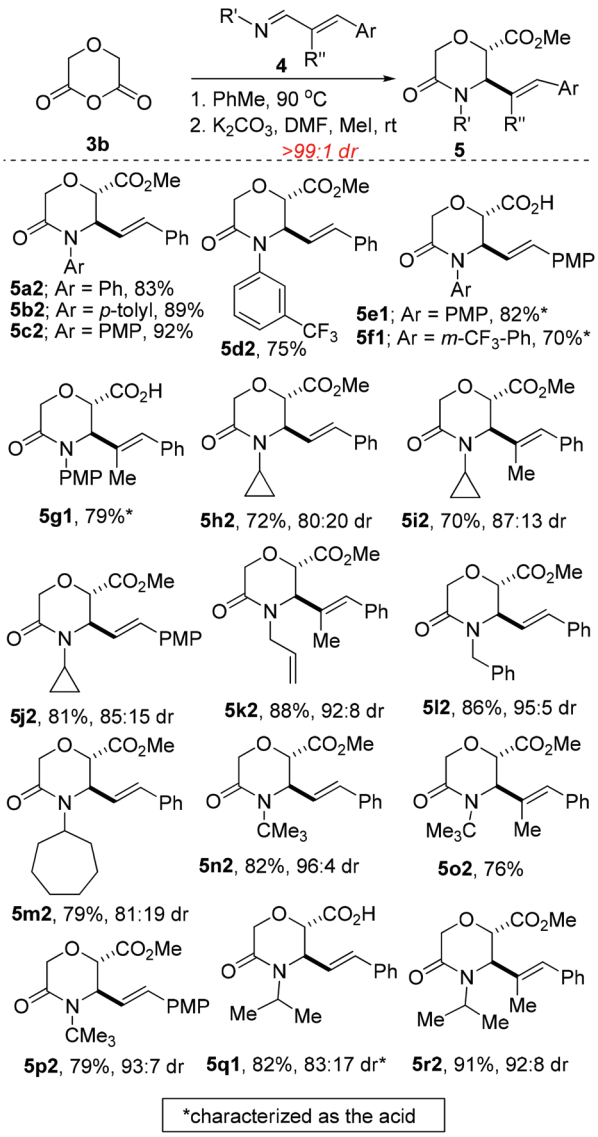


Fig. 3 Examples of hexacyclic anhydrides (*i.e.*, **3**) and 1,3-azadienes (*i.e.*, **4**) employed in these studies.



Scheme 1 Annulation of 1,3-azadienes with diglycolic anhydride.

phenyl (*i.e.*, PMP) group is affordable in impeccable yield and in excellent diastereoselectivity. This is a synthetically appealing result given that in addition to being readily removable (making it a place-holder for other *N*-substituents),[43] the PMP group is amenable to further functionalization under several reaction manifolds, including transition metal-catalyzed cross-couplings of the aryl ether subunit. The amenability of electron-poor 1,3-azadienes of type **4e** to this hexannulation protocol has set the stage for rapid installation of pharmaceutically relevant motifs such as a trifluoromethylaryl group (see **5d2**). *N*-Aryl imino dienes derived from substituted cinnamaldehydes react stereoselectively with diglycolic anhydride (see **5e1** & **5f1**). Importantly, internally substituted *N*-aryl-1,3-azadienes seamlessly undergo productive hexannulation to afford cycloadducts such as **5g1**, without any complications arising from *E*/*Z* isomerization. This result further highlights the merits of our strategy given that *stereodefined* approaches to *trisubstituted styrene* derivatives are at a premium.[44–47]

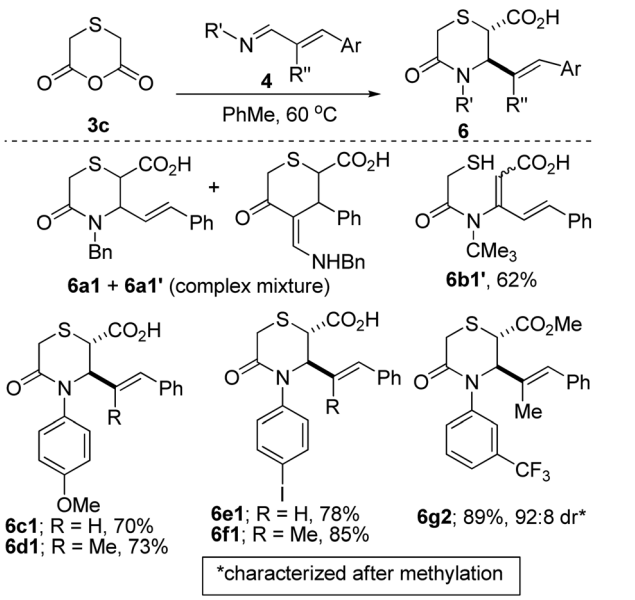
Knowing that the nature of the *N*-substituent present on a morpholine ring can have a dramatic effect on its biological activity, the amenability of 1,3-azadienes bearing nonaryl *N*-substituents to substrate-controlled hexannulation with **3b**, was next explored. Encouragingly, cycloalkyl-, allyl-, benzyl-, isopropyl- and *tert*-butyl-containing imino dienes are all competent reactive partners (see **5h2–r2**).

The relative configuration of the products depicted in Scheme 1 was assigned using NOE and coupling constant analyses, and also by analogy to those of the unambiguously established benzylic counterparts.[42]

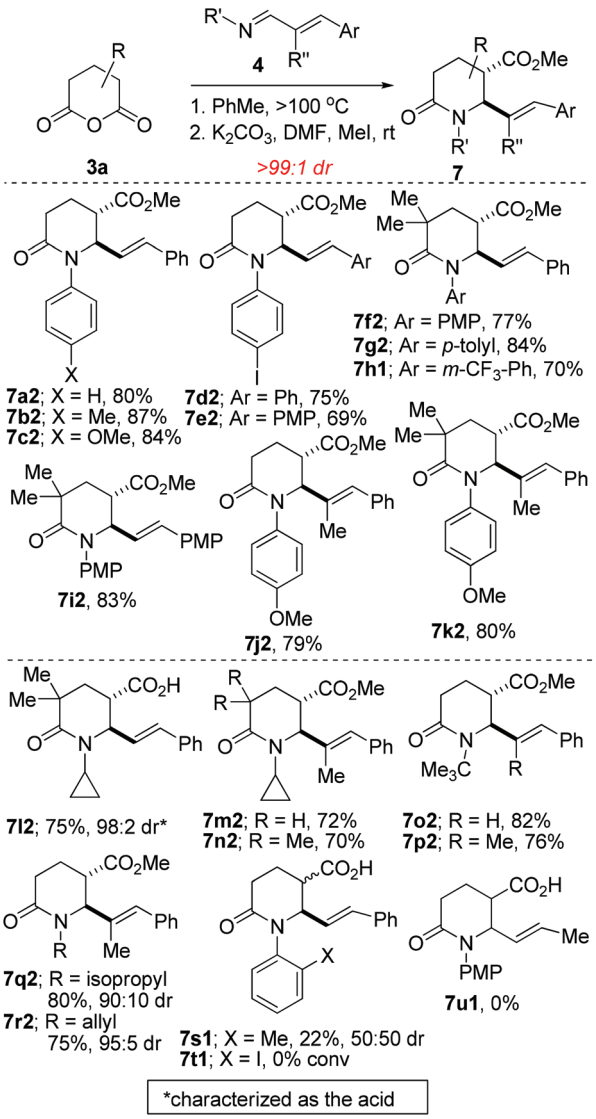
Our studies have revealed that thiodiglycolic anhydride (**3c**), whose α-CH acidity is close to that of homophthalic anhydride (**3f**) displays unproductive reactivity with inherently more reactive *N*-alkyl azadienes, even at 60 °C (see **6a1–6b1′**). Encouragingly, **3c** undergoes satisfactory annulation with *N*-aryl azadienes to afford the allylic thiomorpholinonic acids/esters depicted in Scheme 2 (see **6c1–6g2**).

The aza-hexannulation strategy described herein is not limited to hexacyclic anhydrides bearing an endocyclic heteroatom. This is supported by observations that inert anhydrides **3a**/**d** react satisfactorily with α,β-unsaturated imines, at elevated temperatures, to afford the corresponding piperidinonates depicted in Scheme 3 (see **7a–r**). The amenability of **3d** to this hexannulation protocol has set the stage for the installation of α-amido quaternary centers. In contrast with **3d**, anhydride **3e** fails to furnish the desired cycloadducts, even at 150 °C, presumably due to steric congestion.

Not all α,β-unsaturated imines that we have evaluated react efficiently and stereoselectively with the hexacyclic anhydrides employed in these studies. For instance, *ortho*-substituted



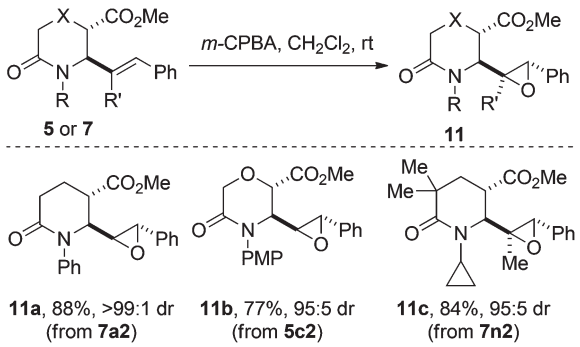
Scheme 2 Annulation of 1,3-azadienes with thiodiglycolic anhydride.



Scheme 3 Annulation of 1,3-azadienes with either glutaric anhydride or 2,2-dimethylglutaric anhydride.

N-aryl-azadienes such as **4w/x** barely react with **3a/b** (see **7s1**, details are in the ESI‡). Additionally, the importance of having the styrenyl motif is highlighted by observations that azadienes derived from *trans*-crotonaldehyde fail to furnish the desired allylic lactams (see **7u1**). In these cases, hydrolysis of the azadiene and concomitant nucleophilic attack of the anhydride by the ensuing amine are observed. Performing the reaction in the presence of molecular sieves fails to negate the hydrolysis.

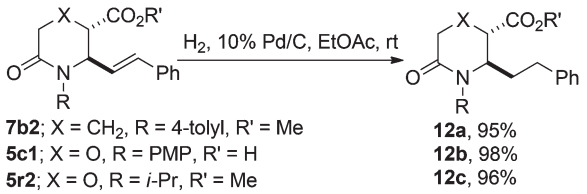
Desiring to broaden the synthetic utility of the aza-hexannulation transformation described herein, we have shown that further elaboration of the cycloadducts to other synthetically important scaffolds is possible. For example, *m*-CPBA-mediated epoxidation of allylic piperidinonate **7a2**, and of morpholinonate **5c2** furnishes epoxylactams **11a** and **11b**, respectively (Scheme 4).



Scheme 4 Epoxidation of allylic lactamoyl esters.

Trisubstituted alkene **7n2** also undergoes effortless face-selective oxa-cyclopropanation and gives rise to epoxide **11c**, which contains four contiguous stereocenters, one of which is tetrasubstituted.

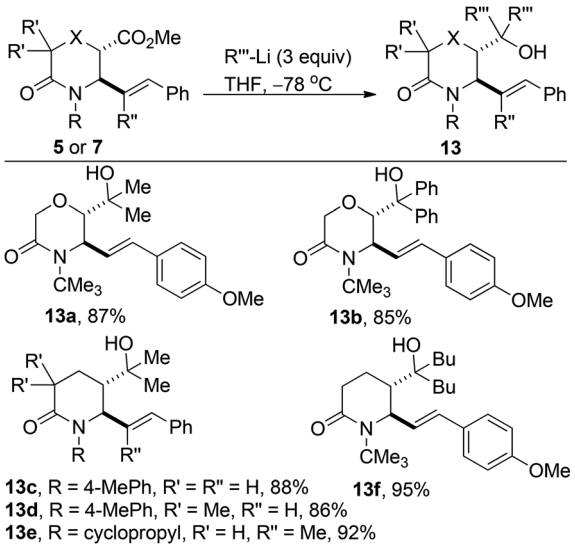
Catalytic hydrogenation of the alkenyl motif resident in functionalized lactams such as **5** and **7** has paved the way for α-arylethylation (Scheme 5, see **12a–c**). This is noteworthy since it is well established that imines derived from enolizable aldehydes such as hydrocinnamaldehyde are incompetent annulative partners for cyclic anhydrides such as **3**, mainly because the latter preferably serve as acylating agents.[42]



Scheme 5 Aryl ethylation of allylic lactams.

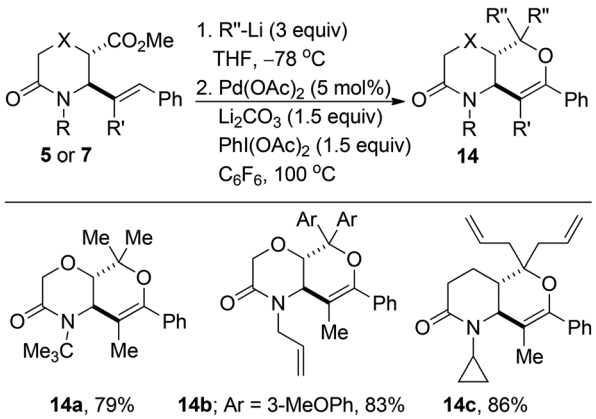
We have found that lactamoyl esters of types **5** and **7** are amenable to substrate-controlled site-selective functionalization with organolithium nucleophiles. For instance, *tert*-butyl-bearing morpholinonate **5n2** reacts chemoselectively with excess methyllithium and phenyllithium to afford tertiary morpholinols **13a** and **13b**, respectively (Scheme 6). Under identical reaction conditions, indiscriminate attack of both the ester and lactam motifs resident in the non *tert*-butyl-bearing morpholinonates depicted in Scheme 1 is observed. However, at this temperature, inherently less reactive piperidinonates react with alkyllithiums exclusively at the ester terminus (see **13c–f**).

The 2-azabicyclic framework constitutes the core and essential structural elements of several pharmaceuticals, alkaloid natural products, ligands and amino acids. Additionally, the motif offers an excellent platform for systematic scaffolding given that it may be transformed to other bioactive N-heterocycles such as quinolones and indoles. We were therefore elated to find that chemoselective addition of organolithium nucleophiles to lactamoyl esters **5i2**, **5o2** and **7p2**



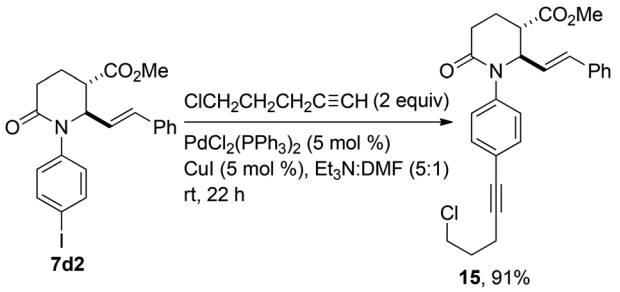
Scheme 6 Substrate-controlled addition of organolithium nucleophiles to allylic lactamoyl esters.

followed by palladium-catalyzed intramolecular etherification furnishes 2-azabicycles **14a–c** in satisfactory efficacy (Scheme 7). In this C–O bond forming process, hydrogen is the only byproduct, thus, making the transformation very atom-economical.



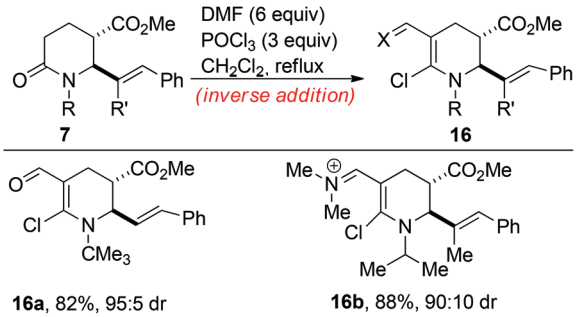
Scheme 7 Pd-catalyzed dehydrogenative cross-coupling.

Intrinsic to our design of installing a 4-iodophenyl substituent on nitrogen was the prospect of utilizing the iodo group as a requisite group for cross-coupling, in view of accessing diversely functionalized arenes. Fittingly, we find that Sonogashira cross-coupling of aryl iodide **7d2** with 5-chloro-1-pentyne proceeds efficiently and affords tethered alkyne **15** (Scheme 8). The choice of alkyne in this example is guided by the possibility of utilizing products such as **15** in subsequent annulative functionalizations, details of which will be disclosed shortly. It is notable that dehydrochlorination and epimerization are not observed under these mild alkynylation conditions.



Scheme 8 Sonogashira cross-coupling of iodide **7d2** with 5-chloro-1-pentyne.

The Vilsmeier–Haack reaction is a notoriously promiscuous transformation from the standpoint of chemoselectivity.[48] It was therefore gratifying to find that site selective, temperature-controlled functionalization of the lactam motif present in allylic lactamoyl ester **7o2**, using the conditions described in Scheme 9 [36,49–51] affords α-chloro-β-formyl dehydropiperidine **16a** in synthetically attractive yield. Of note, efficiency and selectivity are maximized when the Vilsmeier–Haack reagent is generated under refluxing conditions and the lactam is subsequently added at room temperature. In the case of lactam **7q2**, the intermediate chloromethylene iminium salt (*i.e.*, **16b**) is isolated simply by reducing the duration of hydrolysis.



Scheme 9 Regioselective Vilsmeier–Haack reaction of vicinally functionalized allyllic lactamoyl esters.

Conclusions

In summary, 1,3-azadienes have been successfully employed as competent annulative partners with hexacyclic anhydrides, leading to the assembly of a large library of vicinally functionalized and potentially bioactive allylic piperidinonates, morpholinonates and thiomorpholinolinates. The current work stands as an advance over existing methodology given that the construction of **5**, **6** and **7** can be achieved in substrate-controlled, atom-economical, stereoselective, high-yielding, and transition metal-free fashions. The synthetic utility of the methodology has been amply demonstrated through elaboration of the cycloadducts to other versatile azaheterocyclic architectures,

including epoxylactams bearing up to four contiguous stereocenters and 2-azabicyclic motifs.

Experimental

All experiments involving air and moisture sensitive reagents such as palladium precatalysts and organolithium reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ staining. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using DMSO-d_6, CD_3OD or $CDCl_3$ as solvent, at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI$^+$ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

General procedure A: synthesis of 1,3-azadienes

To a round-bottom flask equipped with a stir bar was added the enal (10 mmol), amine (1 to 1.5 equiv.), benzene (50 mL), and anhydrous $MgSO_4$ (2 g). The cloudy suspension was allowed to stir at room temperature. After complete consumption of the amine (based on TLC monitoring), the mixture was filtered through and concentrated under reduced pressure to obtain the crude enamine, which was used in the next step without further purification.

Note: the azadienes need to be stored in the refrigerator when not used immediately.

General procedure B: reaction of 1,3-azadienes with hexacyclic anhydrides

A 5 mL screw-cap vial was flame-dried, evacuated and flushed with nitrogen. A solution of the 1,3-azadiene (1.0 mL, 0.10 M in freshly distilled toluene) was added to the vial at room temperature followed by the cyclic anhydride (1 to 1.1 equiv.). The contents were placed in a pre-heated oil bath thermostatted at the desired temperature (*e.g.*, 90 °C for diglycolic anhydride). After complete consumption of the enal (as judged by TLC and NMR), the mixture/suspension was cooled to room temperature and washed several times with petroleum ether, then concentrated under reduced pressure to afford the crude cycloadducts.

General procedure C: methyl esterification of cycloadducts

To a stirring suspension of the acid (1 mmol), dissolved in DMF (5 mL), and K_2CO_3 (6 equiv.) was added methyl iodide (3 equiv.) under nitrogen atmosphere. The reaction mixture was stirred for 12 to 18 h (TLC monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired ester.

General procedure D: organolithium addition

To the crude lactamoyl ester (1.0 mmol) dissolved in freshly distilled THF (5 mL), was slowly added butyllithium (2.0 mL, 2.0 M solution in hexanes, 4 equiv.) under nitrogen at −78 °C. After complete consumption of the ester (as indicated by TLC and GC-MS), the mixture quenched by slow addition of *sat.* aq NH_4Cl. The mixture was diluted with Et_2O. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: flash chromatography on silica (pretreated with 1% Et_3N).

General procedure E: catalytic hydrogenation

To a round-bottomed flask equipped with a magnetic stir bar was added EtOAc and 10% Pd/C at room temperature. A solution of the alkene in EtOAc was added. The flask was degassed and placed under an inert atmosphere of nitrogen. After complete addition of the alkene, the nitrogen line was cut off. A balloon of H_2 was attached and the reaction mixture was stirred at r.t. After complete consumption of the allylic lactam (based on GC-MS or TLC monitoring), the mixture was filtered through Celite and concentrated under reduced pressure.

General procedure F: epoxidation

To a 10 mL vial, in a 0 °C bath, equipped with a magnetic stir bar under a N_2 atmosphere, was added the allylic lactam (0.50 mmol) and CH_2Cl_2 (5 mL). *m*-CPBA (1.0 mmol, 2 equiv.) was then added in one portion. After being stirred for 16 h, during which time the bath was allowed to expire, the reaction mixture was quenched by the sequential addition of *sat.* $Na_2S_2O_3$(aq) solution (5 mL) along with 10% NaOH solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with 10% NaOH (2 × 5 mL) and with brine. It was then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude epoxide.

General procedure G: palladium-catalyzed etherification

To an oven dried vial equipped with a stir bar was added the crude alcohol, prepared using general procedure D (1.0 mmol) in hexafluorobenzene (5 mL). $Pd(OAc)_2$ (12 mg, 5 mol%), Li_2CO_3 (1.5 mmol, 1.5 equiv.), and $PhI(OAc)_2$ (1.5 mmol, 1.5 equiv.) were then added. The contents were then stirred at 100 °C for the indicated length of time prior to cooling to room temperature. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the crude product, which was directly subjected to flash column chromatography.

General procedure H: Vilsmeier–Haack reaction of allylic lactamoyl esters

To a solution of DMF (6 mmol, 6 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise, phosphorus oxychloride (3 mmol,

3 equiv.). The resulting pale yellow mixture was refluxed for 40 min. A solution of the lactam (1 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was cooled to room temperature and stirred for the indicated time period (TLC and LC-MS monitoring was used to follow the extent of the reaction). Upon completion, the mixture was poured into a large flask containing crushed ice. After stirring at room temperature for 60 min, the layers were separated (note 1). Powdered K_2CO_3 was added slowly to the aqueous layer and the flask was swirled after each addition (**Caution**: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted three times with CH_2Cl_2 and washed with brine. The combined organic layers were dried over Na_2SO_4 for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as an oil.

Note 1: in one instance the organic layer also contained significant amounts of the product.

Synthesis of acid 5e1. Prepared from imine **4f** (267 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv.), using general procedure B. T = 90 °C, time = 18 h. Yield = 314 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (1H, s, br), 7.51 to 6.77 (8H, m), 6.37 to 6.13 (2H, m), 4.81 to 4.20 (4H, m), 3.76 to 3.67 (6H, overlapping singlets). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 167.5, 159.8, 158.9, 136.2, 134.1, 132.2, 130.0, 129.3, 129.1, 128.7, 128.4, 128.3, 128.3, 128.1, 125.4, 122.2, 122.1, 114.2, 114.1, 75.9, 68.1, 64.4, 63.8, 55.4, 55.3. **HRMS-EI$^+$** (m/z): calc'd for $C_{21}H_{21}NO_6$ 383.1369; found 383.1376.

Note: all other acids depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of morpholinonate 5i2. Prepared from imine **4l** (185 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv.) using general procedures B and C. T = 90 °C, time = 12 h. Yield = 221 mg, 70%, 87 : 13 dr. ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 to 7.14 (5H, m), 6.65 (1H, s), 4.60 to 4.15 (4H, m), 3.79 (3H, s), 2.65 to 2.49 (1H, m), 1.89 (3H, s), 1.07 to 0.54 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.3, 136.6, 133.4, 131.6, 130.1, 129.3, 129.0, 128.4, 127.3, 127.2, 126.8, 119.6, 76.8, 74.8, 68.2, 67.6, 65.7, 65.6, 65.1, 52.8, 52.6, 28.6, 28.4, 15.2, 14.4, 8.5, 8.3, 5.7, 5.0. **HRMS-EI$^+$** (m/z): calc'd for $C_{18}H_{21}NO_4$ 315.1471; found 315.1476.

Note: all other esters depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of acid 6c1. Prepared from imine **4b** (237 mg, 1.0 mmol) and thiodiglycolic anhydride (132 mg, 1.0 equiv.), using general procedure B. T = 60 °C, time = 12 h. An analytical sample was obtained after a series of washes with cold petroleum ether. Yield = 258 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (1H, br. S), 7.52 to 7.09 (7H, m), 6.91 to 6.79 (2H, d), 6.58 to 6.32 (2H, m), 4.85 to 4.83 (1H, dd), 3.80 to 3.32 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 168.3, 158.8, 135.8, 134.6, 134.1, 130.8, 129.3, 128.1, 126.9, 122.3, 118.9, 66.6, 55.9, 44.8, 28.3. **HRMS-EI+** (m/z): calc'd for $C_{20}H_{19}NO_4S$ 369.1035; found 369.1039.

Note: all other acids depicted in Scheme 2 were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of thiomorpholinonate 6g2. Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv.) using general procedures B & C. T = 60 °C, time = 22 h. Yield = 387 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 to 7.18 (9H, m), 6.62 (1H, s), 4.93 (1H, d), 3.93 to 3.87 (4H, m), 3.57 to 3.39 (2H, m), 1.96 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.37, 165.93, 152.71, 142.86, 141.45, 136.25, 133.03, 131.15, 130.83, 129.73, 129.70, 129.54, 128.52, 128.32, 127.40, 124.35, 124.31, 124.06, 122.78, 70.83, 53.38, 43.75, 29.05, 18.18. **HRMS-EI$^+$** (m/z): calc'd for $C_{23}H_{20}F_3NO_3S$ 435.1116; found 435.1121.

Synthesis of piperidinonate 7a2. Prepared from imine **4a** and glutaric anhydride (114 mg, 1 equiv.) using general procedures B and C. Temp = 105 °C, time = 18 h. Purification: flash chromatography on silica eluting with hexane/EtOAc (50 : 50 to 0 : 100) then 100% MeOH. Yield = 268 mg, 80% over 2 steps, 95 : 5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 to 7.05 (10H, m), 6.39 (1H, d), 6.15 to 6.09 (1H, dd), 4.92 to 4.89 (1H, d), 3.79 (3H, s), 2.97 to 2.93 (1H, m), 2.73 to 2.61 (2H, m), 2.42 to 2.25 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 169.3, 141.9, 135.8, 134.8, 133.3, 129.1, 128.8, 128.2, 127.7, 127.3, 126.5, 124.4, 63.8, 52.5, 44.5, 29.9, 20.4. **HRMS-EI$^+$** (m/z): calc'd for $C_{21}H_{21}NO_3$ 335.1521; found 335.1525.

Note: all other esters depicted in Scheme 3 were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of epoxylactam 11a. Prepared from allylic lactam **7a2** (0.50 mmol) using general procedure F. Purification: flash chromatography on silica eluting with hexane/EtOAc (50 : 50 to 0 : 100). Yield = 155 mg, 88%, >99 : 1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 to 7.10 (8H, m), 6.91 to 6.86 (2H, d), 4.01 (1H, d), 3.81 (3H, s), 3.28 to 3.25 (1H, d), 3.17 to 3.15 (1H, dd), 2.69 to 2.35 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 168.4, 141.5, 135.5, 133.2, 129.7, 129.6, 129.3, 128.6, 128.5, 128.4, 128.0, 127.6, 125.3, 63.7, 61.9, 60.3, 52.7, 40.7, 29.5, 20.0. **HRMS-EI$^+$** (m/z): calc'd for $C_{21}H_{21}NO_4$ 351.1471; found 351.1475.

Note: epoxides **11b** and **11c** (see Scheme 4) were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of alkylated lactam 12a. Prepared from alkene **7b2** (0.50 mmol) using general procedure E. Yield = 167 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 to 7.13 (7H, m), 7.02 (2H, d), 4.30 to 4.20 (1H, m), 3.79 (3H, s), 2.80 to 2.71 (1H, t), 2.65 to 2.16 (9H, m), 2.10 to 1.979 (1H, m), 1.83 to 1.79 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 169.1, 140.5, 138.9, 137.0, 129.9 129.9, 128.5, 128.4, 128.2, 128.1, 127.6, 127.3, 126.2, 126.1, 61.0, 52.5, 41.3, 34.6, 31.9, 29.7, 21.2, 19.9. **HRMS-EI$^+$** (m/z): calc'd for $C_{22}H_{25}NO_3$ 351.1834; found 351.1839.

Note: alkanes **12b** and **12c** (see Scheme 5) were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of tertiary alcohol 13a. Prepared from ester **5p2** (0.50 mmol) and MeLi (1.42 mL, 1.4 M solution in THF, 2 mmol, 4 equiv.) using general procedure D. Yield = 151 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d), 6.84 (2H, d), 6.41 (1H, d), 5.97 to 5.91 (1H, dd), 4.69 to 4.66 (1H, dd), 4.17

(1H, d), 3.95 (1H, d), 3.79 (3H, s), 3.58 (1H, d), 2.29 (1H, s), 1.44 to 1.24 (9H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 159.6, 132.0, 130.5, 130.4, 130.0, 128.7, 127.9, 127.8, 127.6, 125.6, 125.0, 114.2, 114.0, 113.7, 85.0, 84.1, 80.0, 77.4, 77.1, 76.8, 72.9, 71.2, 68.7, 68.0, 57.9, 55.7, 55.4, 55.2, 53.8, 30.4, 30.0, 28.8, 28.5, 28.4, 28.4, 28.0, 27.3, 26.7, 26.4, 26.2, 25.6, 14.3. **HRMS-EI$^+$** (*m*/*z*): calc'd for $C_{20}H_{29}NO_4$ 347.2097; found 347.2095.

Note: alcohols **13b–f** (see Scheme 6) were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of bicyclic enol ether 14a. Prepared from ester **5o2** (0.50 mmol) using general procedures D and G. Yield = 149 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 to 7.22 (5H, m), 4.53 (1H, d), 4.31 to 4.11 (2H, dd), 3.51 (1H, d), 1.88 (3H, s), 1.54 to 1.30 (15H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 138.4, 137.0, 128.9, 128.5, 128.4, 128.3, 127.0, 81.5, 77.4, 77.3, 77.1, 76.8, 73.4, 67.4, 59.1, 58.5, 30.4, 29.8, 28.2, 27.8, 27.2, 26.3, 15.2. **HRMS-EI$^+$** (*m*/*z*): calc'd for $C_{20}H_{27}NO_3$ 329.1991; found 329.1996.

Note: cyclic enol ethers **14b** and **14c** (see Scheme 7) were prepared as described above. Spectroscopic data can be found in the ESI.‡

Synthesis of alkyne 15. To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added aryl iodide **7d2** (461 mg, 1 mmol, 1.0 equiv.) in DMF/Et_3N (5 : 1 mL) and 5-chloro-1-pentyne (0.212 mL, 2 mmol, 2 equiv.), under nitrogen atmosphere. After completely degassing the flask, $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) and CuI (10 mg, 5 mol%) were added rapidly and concurrently. The mixture was then stirred at room temperature for 22 h (as indicated by TLC and GC-MS). Upon completion, the mixture was concentrated under reduced pressure and directly subjected to flash chromatography on silica eluting with hexane/EtOAc. Yield = 396 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 to 7.16 (9H, m), 6.41 to 6.37 (1H, d), 6.18 to 6.06 (1H, dd), 4.89 to 4.86 (1H, dd), 3.78 to 3.63 (5H, m), 2.93 to 2.86 (2H, m), 2.65 to 2.51 (4H, m), 2.34 to 2.18 (2H, m), 2.03 to 1.97 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.2, 141.3, 135.7, 134.9, 133.4, 132.3, 128.7, 128.4, 127.5, 127.3, 126.7, 124.3, 122.5, 88.7, 81.1, 63.6, 52.5, 44.7, 43.8, 31.4, 29.7, 21.1, 16.9. **HRMS-EI$^+$** (*m*/*z*): calc'd for $C_{26}H_{26}ClNO_3$ 435.1601; found 435.1609.

Synthesis of chloro dehydropiperidinal 16a. Prepared from lactam **7o2** (1.0 mmol) using general procedure H. Yield = 296 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (1H, s), 7.34 to 7.23 (5H, m), 6.47 to 6.44 (1H, d), 6.04 to 5.98 (1H, dd), 5.17 to 5.07 (1H, dd), 3.78 (3H, s), 2.90 to 2.87 (2H, m), 2.46 to 2.34 (1H, m), 1.56 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 172.4, 150.0, 135.8, 134.2, 132.2, 128.9, 127.1, 126.6, 124.6, 110.5, 61.7, 59.3, 52.3, 43.6, 34.8, 31.6, 21.0. **HRMS-EI$^+$** (*m*/*z*): calc'd for $C_{20}H_{24}ClNO_3$ 361.1145; found 361.1149.

Synthesis of chloro iminium ion 16b. Prepared from lactam **7q2** (1.0 mmol) using general procedure H, but hydrolysis was carried out for only 20 min and no basification was necessary. Yield = 342 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, s), 7.38 to 7.21 (5H, m), 6.06 (1H, s), 4.98 to 4.90 (1H, m), 4.70 to 4.66 (1H, d), 3.76 to 3.61 (9H, m), 3.28 to 3.16 (2H, m), 2.86 to 2.80 (1H, dd), 1.88 (3H, s), 1.38 to 1.25 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 162.3, 157.5, 136.1, 135.4, 128.9, 128.1, 127.9, 127.4, 97.2, 62.3, 58.4, 56.6, 52.8, 41.9, 38.2, 23.2, 21.4, 20.1, 16.7. **HRMS-EI$^+$** (*m*/*z*): calc'd for $C_{22}H_{30}Cl_2N_2O_2^+$ 381.1990; found 381.1994.

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