JOC The Journal of Organic Chemistry

Article

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Experimental Studies on the Selective β-C−H Halogenation of Enones

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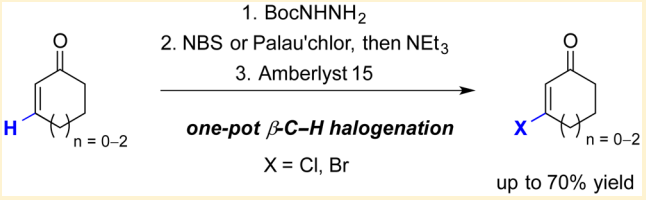
Supporting Information

ABSTRACT: Here we describe the realization of a one-pot protocol for the β-C−H halogenation of cyclic enones via umpolung of the β-carbon. The developed method includes hydrazone formation and selective β-halogenation (bromination, chlorination) with *N*-bromosuccinimide and Palau'chlor (2-chloro-1,3-bis(methoxycarbonyl)guanidine) followed by hydrolysis of the hydrazone moiety. Using the optimized conditions, we were able to effectively β-brominate and β-chlorinate for the first time cyclic enones with different substitution patterns and various functional groups in one flask, whereas previous methods for this transformation required several steps. Additionally, the utility of the method was demonstrated in a short synthesis of the core structure of the *Aspidosperma* alkaloid jerantinine E.



INTRODUCTION

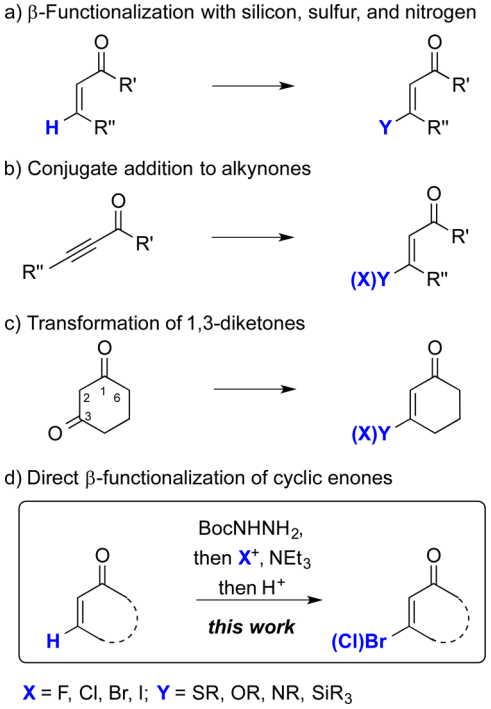
Enones containing a heteroatom at their β-position are of high importance in organic synthesis and have found widespread application as versatile building blocks in transformations such as Diels−Alder reactions and conjugate addition processes. Although several strategies have been developed for the synthesis of β-carbon and β-heteroatom substituted α,β-unsaturated compounds, synthetic methods for the direct production of β-halogenated conjugated systems are somewhat limited. In general, these functionalized compounds can be prepared from simple α,β-unsaturated compounds, alkynones, and 1,3-diketones (Scheme 1).

The β-functionalization of α,β-unsaturated compounds such as enones can only be achieved with carbon,[1] silicon,[2] sulfur,[3] and nitrogen,[4] but not with halogens (Scheme 1a). Considering that the α-iodination of enones (I_2, pyridine) has become a routine transformation[5] and that the indirect methods described above are often not practical, it is surprising that a general protocol for the direct β-C−H halogenation has not yet been reported.

The ability of alkynones to undergo 1,4-addition with metal and trimethylsilyl halides[6] is mainly restricted to acyclic systems and leads to the formation of double bond isomers (Scheme 1b). Similar products are obtained from the Lewis acid catalyzed Friedel−Crafts-type acylation of terminal alkynes using gallium(III) chloride,[7] iron(III) chloride,[8] or aluminum-(III) chloride[9] and the iridium-catalyzed version of this transformation to selectively give (*Z*)-β-chloro-α,β-unsaturated ketones was reported by Tsuji.[10]

Six-membered 1,3-diketones with substituents at C5 or C2 can be converted to the β-chloro ($POCl_3$, DMF), β-bromo (Br_2, PPh_3, NEt_3), β-iodo (I_2, PPh_3, NEt_3),[11] and β-fluorinated (*N*,*N*-diethyl-α,α-difluoro-*m*-methylbenzylamine)[12] enones with high regioselectivity (Scheme 1c). However, conversion of unsymmetrical and C6-substituted 1,3-diketones to β-substituted α,β-unsaturated carbonyl compounds is typically unselective and affords product mixtures.[11a]

Scheme 1. Strategies for the Synthesis of β-Functionalized Enones



Received: December 11, 2014
Published: January 26, 2015

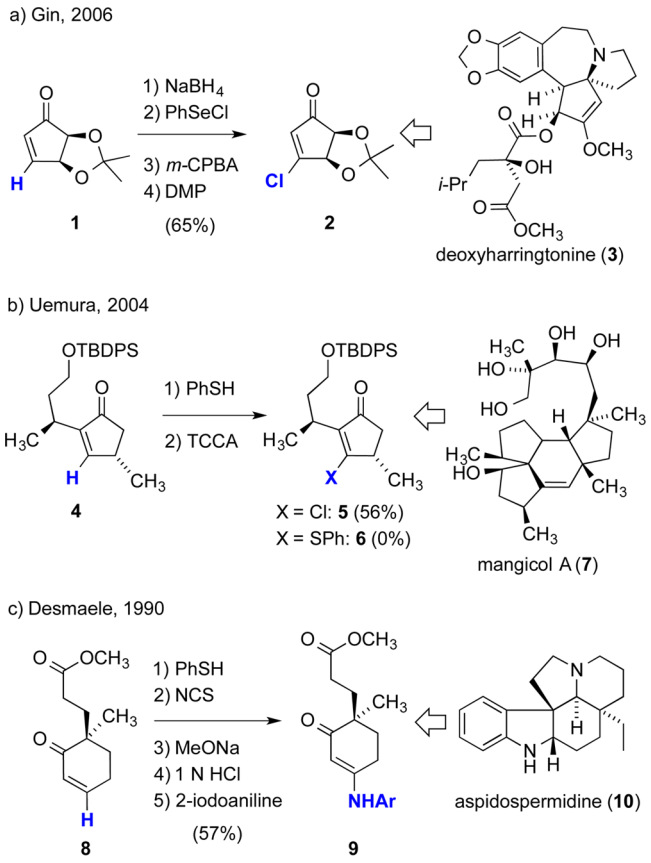
DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

The difficulty in accessing β-halogenated enones limit their synthetic utility. For instance, the β-chlorination of enones such as **1** generally requires a minimum of four individual steps, including two nonstrategic redox manipulations. An application of this procedure was reported by Gin (Scheme 2a) during the synthesis of the cyclopentenone fragment **2** of deoxyharringtonine (**3**).[13] To the best of our knowledge, only a single example for which a two-step protocol could be realized is reported to date (Scheme 2b). Based on seminal work by Bakuzis for the oxidative β-functionalization of enones with sulfur,[3a] Uemura envisioned the synthesis of the mangicol A (**7**) building block **5** using the original four-step protocol.[14] Although conjugate addition of thiophenol proceeded as described, treatment of the intermediate 1,4-adduct with trichloroisocyanuric acid (TCCA) did not give the expected Pummerer-type product **6** but directly produced **5** in 79% yield.

The authors noted, "There are no published procedures for the direct β-halogenation of cyclopentenones, and thus this reaction was regarded as a promising strategy for the β-chlorination of enones". Surprisingly, a detailed analysis of this unusual reaction pathway has never been disclosed.

Another example where direct β-C−H halogenation could improve step-economy is Desmaele's synthesis of the aspidospermidine model system **9** (Scheme 2c). For this component, five individual steps were necessary to generate the β-enaminone.[15] Realization of a selective β-halogenation of **8** would reduce the synthetic effort to a simple coupling reaction with *o*-iodoaniline.

Scheme 2. β-C−H Functionalization of Enones in Natural Product Synthesis



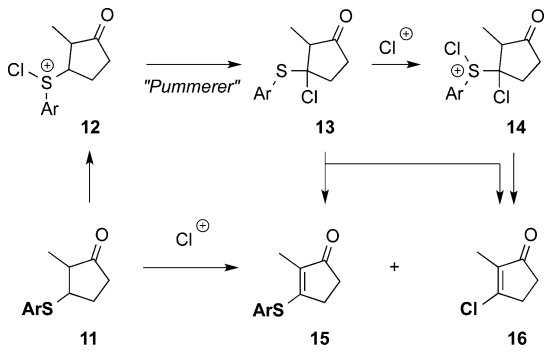
In fundamental work by Severin, it was shown that chlorination, bromination, and iodination of α,β-unsaturated hydrazones,[16] semicarbazones, and oximes[17] regioselectively afford the C3 halogenated products in moderate yields. When analyzing Severin's reported sequence in more detail, we realized that (1) the introduction of the hydrazones was impractical due to the necessity of elevated temperatures in combination with long reaction times, (2) both the hydrazone and the halogenated product had to be isolated due to the incompatibility of the solvents and reaction conditions used for each individual step, (3) harsh conditions (hydrobromic acid, aqueous formaldehyde) were involved for the cleavage of the hydrazone, and (4) some of the used reagents were expensive (2-methyl-benzothiazolinone hydrazone) or inherently incompatible with aprotic organic solvents (semicarbazide). Owing to these drawbacks and in light of the lack of practical alternatives, it was our goal to develop a conceptually similar method that benefits from operational simplicity and better overall efficiency.

Herein, we report the development of a one-pot β-C−H halogenation protocol as one possible solution for this neglected transformation. While bromination of cyclic enones containing various functional groups was efficiently mediated by *N*-bromosuccinimide (NBS), for the chlorination reactions we took advantage of the unique reaction profile of the recently developed reagent Palau'chlor (CBMG, 2-chloro-1,3-bis-(methoxycarbonyl)guanidine).[18]

RESULTS AND DISCUSSION

The Pummerer Approach. Initial attempts to adapt the serendipitous discovery of Uemura for the Pummerer-type[19] β-halogenation of enone **7** and develop a general method were unsuccessful. Though the reaction of various arylthiols with 2-methylcyclopent-2-en-1-one afforded the 1,4-adduct **11**, further oxidation with *N*-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or Selectfluor as the oxidants, both in the presence and in the absence of base (triethylamine) led to the formation of either the β-phenylthio enone **15**[3a] or complex product mixtures (Scheme 3). We hypothesized that increasing the oxidant loading beyond equimolar amounts should allow us to oxidize the speculative intermediate **13** to the chlorosulfonium salt **14**. However, all efforts to address this challenge and adapt the conditions of Uemura for the synthesis of **16** were met with failure. Consequently, we decided to explore an alternative strategy and work on the use of hydrazones as umpolung reagents.

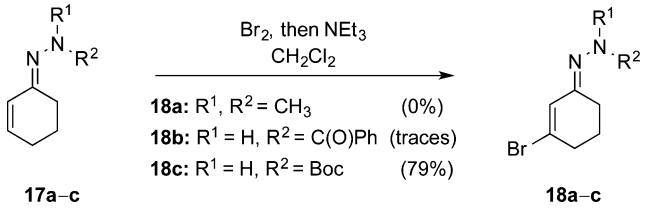
Scheme 3. Initial Working Model for the Conversion of β-Arylthio Ethers to Enones



DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

Halogenation of Hydrazones. For the success of a one-pot β-C−H halogenation protocol, the hydrazone was required to meet several criteria. Its hydrazine precursor must be readily available, soluble in aprotic solvents, inexpensive, and simple to install, while the hydrazone should be amenable to mild hydrolysis.[20] We began our investigations with a survey of commercially available reagents, and selected the hydrazones formed by the condensation of cyclohex-2-en-1-one and *N,N*-dimethylhydrazine, benzoylhydrazine (benzohydrazide), and *tert*-butyl carbazate (*tert*-butoxycarbonyl hydrazide, $BocNHNH_2$) for an initial reaction screen (Scheme 4).

Scheme 4. Bromination of Selected Hydrazones

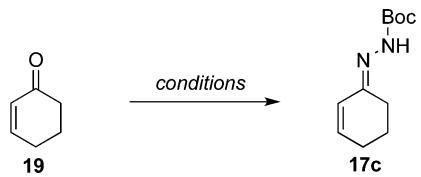


Exposure of **17a−c** to the halogenation conditions revealed that subtle differences in R^1 and R^2 had a profound effect on the halogenation step. First, we focused on the halogenation of *N,N*-dimethyl hydrazone **17a** following the procedure of Severin. We observed that halogenation of **17a** using either *N*-chlorosuccinimide (NCS) or bromine at various temperatures followed by the addition of triethylamine only led to decomposition.[21]

We then investigated the effect of electron-deficient hydrazones on the halogenation step. For benzoylhydrazone derivative **17b**, product formation could only be observed in trace amounts. Slightly adjusting the electronic nature of the hydrazone by exchanging the benzoyl unit for the less electron-withdrawing *tert*-butyloxycarbonyl group had a significant impact on the reaction. Under otherwise identical reaction conditions (1.0 equiv of Br_2, 2.0 equiv of NEt_3, CH_2Cl_2, −10 °C), bromination of **17c** afforded β-bromo hydrazone **18c** in 79% yield.

Hydrazone Formation. Moving on from these initial observations, our next goal was to establish an experimental protocol that would allow us to run the overall β-C−H halogenation in one single flask. Therefore, we first investigated different methods for the hydrazone formation and their compatibility with the bromination step (Table 1). As illustrated below, acid-catalyzed condensation of cyclohex-2-en-1-one with *tert*-butyl carbazate afforded the condensation product **17c** in low quantities. However, addition of the desiccants magnesium sulfate or sodium sulfate to a solution of both components in refluxing 1,2-dichloroethane furnished **17c** in excellent yields (95−99%).

Table 1. Conditions for the Formation of Hydrazone 17c



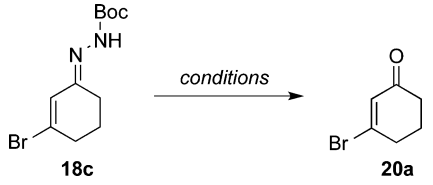
$BocNHNH_2$	additive	solvent	T [°C]	yield (%)[a]
1.00 equiv	AcOH	MeOH	60	48
1.50 equiv	$MgSO_4$	1,2-dichloroethane	85	99
1.05 equiv	Na_2SO_4	1,2-dichloroethane	85	95

[a]Yields of isolated products.

With a practical condensation protocol in hand, we tested different batches of crude **17c** for the bromination step. In this context, we noticed that excess *tert*-butyl carbazate was detrimental to the bromination step. Surprisingly, while the condensation required an excess of *tert*-butyl carbazate in the presence of magnesium sulfate, only equimolar amounts were needed when sodium sulfate was used. Therefore, the sodium sulfate promoted condensation reaction protocol was used for further investigations of the one-pot procedure.

Hydrolysis of the Hydrazone. Next, we examined various conditions for the hydrolysis of the hydrazone. A selection of reagent combinations is shown in Table 2. Attempted cleavage of **18c** with oxalic acid resulted in no conversion, and the use of copper(II) bromide led to the formation of complex product mixture. Exposure of **18c** to hydrobromic acid afforded β-bromo enone **20a** in low yield. The use of trifluoroacetic acid in combination with aqueous formaldehyde showed some improvement and provided **20a** in 56% yield. After further optimization, we found that treating a solution of **18c** in acetone−water (v/v = 9:1) with commercially available and inexpensive Amberlyst 15 at 60 °C reproducibly afforded **20a** in good yield. The use of Amberlyst 15 not only gave superior yields but also facilitated a non-aqueous workup procedure to ensure that no product was lost during reaction workup.

Table 2. Screening of Conditions for the Hydrazone Hydrolysis



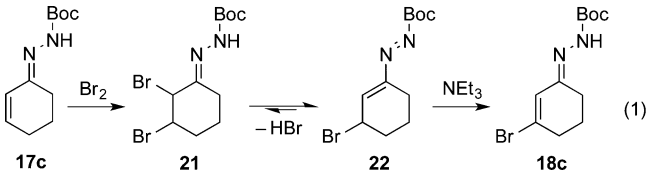
entry	additive	solvent	T [°C]	yield (%)[a]
1	oxalic acid	CH_2Cl_2, H_2O	25	0
2	$CuBr_2$	CH_2Cl_2, H_2O	25	0
3	HBr	THF, H_2O	25	26
4	TFA, CH_2O	THF, H_2O	25	56
5	Amberlyst 15	acetone, H_2O	60	70

[a]Yields of isolated products.

The One-Pot Protocol. After having established an effective method for the conversion of **17c** to **20a**, we investigated the one-pot protocol by combining the previously optimized conditions (*tert*-butyl carbazate, Na_2SO_4; Br_2, NEt_3; Amberlyst 15) into a single flask. A first attempt to convert cyclohex-2-en-1-one to 3-bromocyclohex-2-en-1-one (**20a**) gave a 60% overall yield. Careful analysis of the crude reaction mixture revealed the α-brominated product as the major side product (β/α = 10:1). We believe that bromination of hydrazone **17c** initially affords the dibromide **21** (efforts to isolate **21** resulted in complex product mixtures), which then eliminates to afford allylic bromide **22** (eq 1).[19] Conversion to the β-brominated hydrazone **19c** occurs upon treatment with triethylamine. Elimination of the β-bromine substituent in **21** presumably leads to the undesired α-brominated product.

Addition of silver(I) salts (Ag_2O, Ag_2CO_3) had no effect on the observed regioselectivity, whereas lowering the reaction

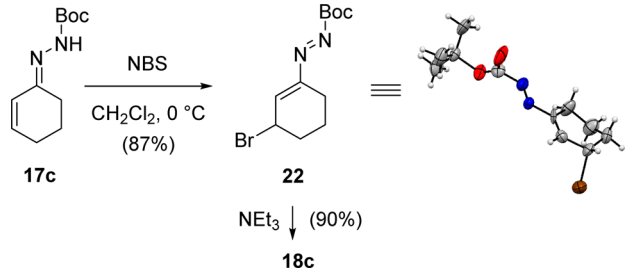
DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294



temperature to −10 °C moderately decreased the amount of α-brominated product (β/α = 20:1). However, this strategy was found to be impractical due to solidification of the reactant solution in dichloromethane at temperatures below −5 °C.

In an effort to overcome these limitations, less reactive, electrophilic brominating reagents were investigated for this transformation. Thus, treatment of **17c** with 1 equiv of *N*-bromosuccinimide (NBS) resulted in the formation of the allylic bromide **22**, which could be isolated and characterized by X-ray crystallography (Scheme 5). Addition of triethylamine to

Scheme 5. Formation of Allylic Bromide 22 and Its Conversion to 18c

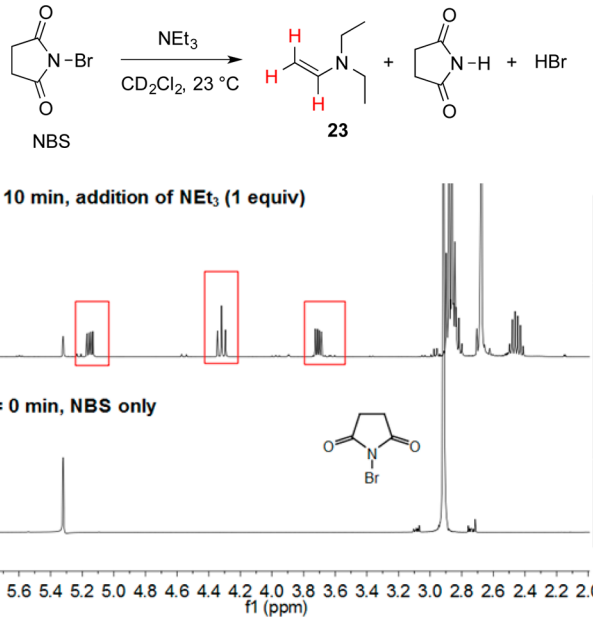


pure **22** cleanly promoted the isomerization to **18c** (90%). Surprisingly, when this transformation was repeated by simultaneously adding NBS and triethylamine, only low conversion was observed. Monitoring the reaction via ^{1}H NMR spectroscopy revealed that triethylamine was converted to the unstable enamine **23** (Scheme 6).[22] Consecutive addition of both reagents completely suppressed this side reaction.

Chlorination. With a practical one-pot bromination protocol in hand, we were tempted to introduce a β-chlorine substituent by simply exchanging NBS for NCS. To our dismay, this strategy proved to be unsuccessful, and no reaction was observed (Table 3, entries 1 and 2). Further studies therefore focused on the screening of different electrophilic chlorinating reagents. Reagents with modified reactivity such as *N*-chlorophthalimide (NCPhth) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) resulted in a sluggish conversion (Table 3, entries 4 and 5). Even at higher temperatures, only trace amounts of chlorinated products could be isolated from the reaction mixture. While the application of NCS, DCDMH, and NCPhth as chlorenium source for this transformation was mainly limited by their low reactivity, reagents such as TCCA and *N*-chlorosaccharin (NCSacch) exhibited low regioselectivity and afforded allylic chloride **24** as a mixture of unidentified products (entries 6 and 7).[23]

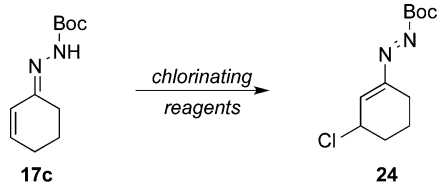
Recently, the Baran group reported a novel guanidine-based electrophilic chlorinating reagent, Palau'chlor, which was shown to be highly efficient and regioselective for the chlorination of a variety of heterocycles, enol ethers, and sulfonamides.[18] Interestingly, upon exposure of hydrazone **17c** to 1 equiv of Palau'chlor, only partial conversion was observed. However, increasing the reagent loading to 2 equiv led to full

Scheme 6. Monitoring the Oxidation of Triethylamine with NBS via ^{1}H NMR Spectroscopy (400 MHz, CD_2Cl_2, 23 °C)[a]



[a]Conditions: 0.08 mmol scale, 1 equiv of NBS, 1 equiv of triethylamine, *c* = 0.1 M in CD_2Cl_2.

Table 3. Screening of Electrophilic Chlorinating Reagents[a]



entry	reagent	*T* [°C]	*t* [h]	yield (%)[b]
1	NCS (1.1 equiv)	0	1	0
2	NCS (1.1 equiv)	50	24	0
3	CuCl (1.1 equiv), NCS (1.1 equiv)	25	24	0
4	DCDMH (2.1 equiv)	50	24	<10
5	NCPhth (1.2 equiv)	23	16	<10
6	TCCA (1.0 equiv)	23	2	12[c]
7	NCSacch (2.1 equiv)	0	1.5	<10
8	**Palau'chlor (2.0 equiv)**	**0**	**1**	**63**[c]

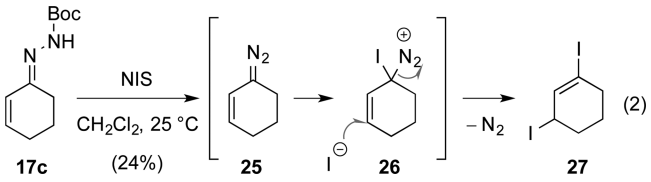
[a]All reactions were performed on a 0.1 mmol scale in dichloromethane (*c* = 0.2 M). [b]Yields determined by ^{1}H NMR using mesitylene as internal standard. [c]Yields of isolated products.

consumption of the starting material, and allylic chloride **24** could be isolated in 63% yield (Table 3, entry 8). Although the highest regioselectivity was achieved using Palau'chlor, dichlorination of the double bond (<20%) and *N*-chlorination of the hydrazone were also observed (<10%). An attempt to suppress the latter reaction by deactivating the hydrazone using trifluoroacetic acid was unsuccesful, and regioselective formation of the α-chlorinated product prevailed.

Iodination and Fluorination. In sharp contrast to the reported bromination and chlorination reactions, iodination and fluorination were exceptionally challenging and proved to be unsuccessful for **17c**. From the complex mixture of iodination products obtained, we were only able to isolate and characterize light-unstable diiodide **27**. According to

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

Barton's seminal work on the oxidation of hydrazones with iodine,[24] a possible reaction pathway leading to the observed product is presented below (eq 2). After oxidation of **17c** to



diazo-intermediate **25**, excess NIS serves to activate the conjugated system to form **26**. This highly reactive intermediate is believed to undergo a S_N2'-type attack of iodide with concomitant loss of dinitrogen to give **27**.

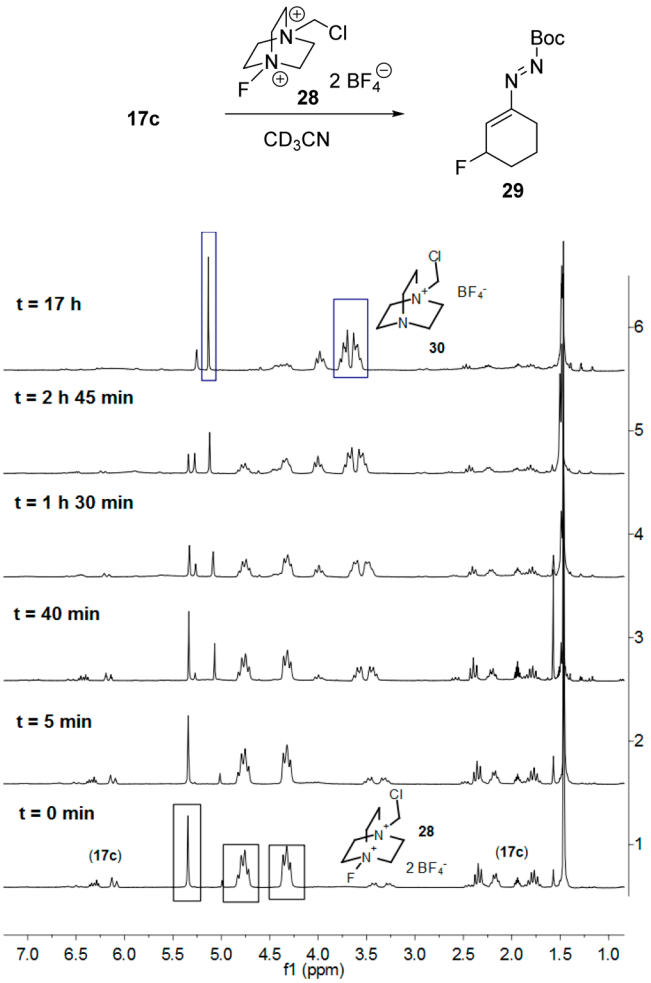
A screen of reaction conditions for the β-fluorination showed that a similar pathway might be operative for the fluorination reaction. While the use of NFSI (*N*-fluorobenzenesulfonimide), Togni's fluoroiodinane,[25,26] or 1-fluoropyridinium tetrafluoroborate only resulted in decomposition of **17c**, the reaction with Selectfluor (**28**) was difficult to rationalize. Monitoring the fluorination of **17c** via ^{1}H NMR spectroscopy in CD_3CN clearly showed a constant transfer of F^+ from Selectfluor and simultaneous formation of **30** (Scheme 7).

From the outset, the substrate (1 equiv) to reagent (1.1 equiv) ratio was lower, as theoretically expected. This observation might be a result of decomposition induced by unselective fluorination. Although full consumption of the starting material occurred within 3 h, only trace amounts (<2%) of fluoride **29** could be isolated from the reaction mixture and characterized. No new signals of the desired product could be detected, and all attempts to directly form the vinyl fluoride by adding different bases (NEt_3, K_2CO_3, pyridine, DABCO) have met with failure so far.

Substrate Scope. To examine the generality of the developed β-C–H bromination and chlorination protocols, we next explored the substrate scope. By this one-pot strategy, a series of cyclic enones with different substitution patterns and various functional groups could be successfully converted to the corresponding β-halo enones (Table 4, see Experimental Section for the synthesis of the enones). The β-bromination of 4- or 5-substituted and 4,4- or 5,5-disubstituted cyclohexenones afforded the products in good yields (**31**–**39**). This included esters, nitriles, protected or free alcohols, alkynes, and trifluoromethyl substituents, showing that various functional groups are tolerated under these mild reaction conditions. For substrates containing substituents at C5 (**40**–**43**) or C6 (**44**), the yield was lower, as expected. While the influence of the C5 substitution was not obvious to us, the dependence of reaction times on the steric demand at C2 or C6 was less surprising. We noted that the condensation reactions of *tert*-butyl carbazate with these substrates did not proceed to full conversion even at prolonged reaction times or higher reaction temperatures.

We also explored the possibility of extending this transformation to five- or seven-membered cyclic enones. This endeavor was moderately successful for cyclohept-2-en-1-one (**45**) and virtually impossible for simple cyclopent-2-en-1-one. However, introduction of a substituent at C2 of the five-membered ring gave access to the β-brominated product **46**. In all cases, the yields for the β-chlorination of these substrates were lower compared with the β-bromination due to the occurrence of *N*-chlorination and dichlorination. Exposure of bicyclic substrates to the one-pot protocol was problematic due

Scheme 7. Reaction Monitoring via ^{1}H NMR Spectroscopy (400 MHz, CD_3CN, 23 °C)[a]



[a]Conditions: 0.1 mmol scale, 1 equiv of hydrazone **17c**, 1.1 equiv of Selectfluor, c = 0.07 M in CD_3CN.

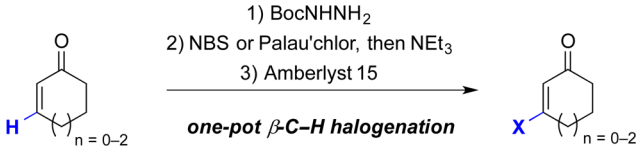
to a low yielding condensation step, and no product formation was observed for **47** and **48**. Similar restrictions were observed for the conversion of an α-chloro enone to **49**. The use of acyclic ketones such as benzylideneacetone resulted in the formation of a complex product mixture, and substrates containing acid sensitive groups were not tolerated under the reaction conditions used for hydrazone cleavage.

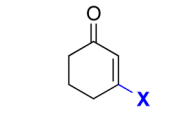
Interestingly, when *trans*-cinnamaldehyde was subjected to the standard one-pot β-C–H halogenation protocol, the conjugated 5-substituted 1,3,4-oxadiazolin-2-one **50** was formed as the major product (Table 5).[27] The desired β-halogenated product could be only observed in trace amounts. We also found that oxidation of the intermediate azomethine carbon atom was more efficient using Palau'chlor instead of NBS. Selected examples for this transformation are illustrated in Table 5.

Synthesis of the Tricyclic Core of Jerantinine E. Using the developed conditions for the β-C–H halogenation, a short and modular synthesis of the tricyclic core structure of the *Aspidosperma* alkaloid jerantinine E (**57**) was accomplished (Scheme 8). This allowed us to circumvent a five-step β-amination procedure as reported by Desmaele (Scheme 2c). Enone **53** was readily available via a Stork–Danheiser alkylation

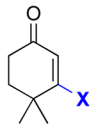
DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281–2294

Table 4. Substrate Scope for the β-C−H Halogenation of Cyclic Enones[a]

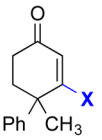




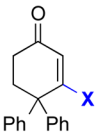
20a X = Br: 55%
20b X = Cl: 26%



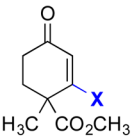
31a X = Br: 68%
31b X = Cl: 26%



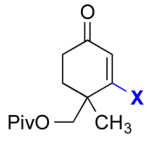
32a X = Br: 70%
32b X = Cl: 22%



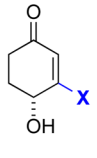
33a X = Br: 63%
33b X = Cl: 18% (21%)[b]



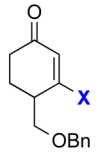
34a X = Br: 70%
34b X = Cl: 34%



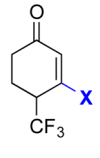
35a X = Br: 59%
35b X = Cl: 24% (32%)[b]



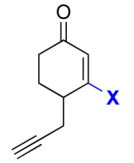
36 X = Br: 27%



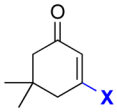
37a X = Br: 52%
37b X = Cl: 20%



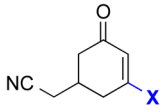
38 X = Br: 52%



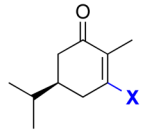
39a X = Br: 47%
39b X = Cl: 30%



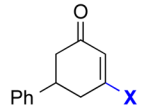
40 X = Br: 39%



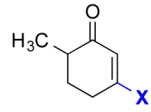
41 X = Br: 31%



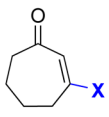
42 X = Br: 33%



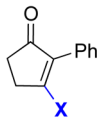
43a X = Br: 45%
43b X = Cl: 36%



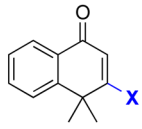
44a X = Br: 34%
44b X = Cl: 22%



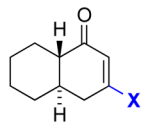
45a X = Br: 28%
45b X = Cl: (8%)[b]



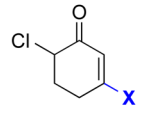
46 X = Br: 43%



47 X = Br: 0%



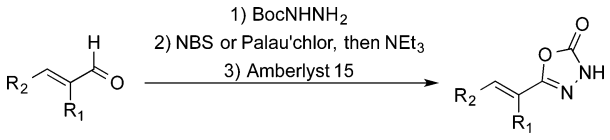
48 X = Br: 0%

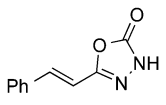


49 X = Br: 0%

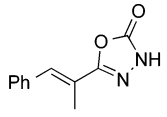
[a]All yields refer to the one-pot protocol: (1) *tert*-butyl carbazate (1.05 equiv), Na_2SO_4 (3.10 equiv), $Cl(CH_2)_2Cl$ (c = 0.8 M), 85 °C; (2) NBS (1.05 equiv) or Palau'chlor (2.00 equiv), 0 °C, 1 h, NEt_3 (3.30 equiv), 23 °C, CH_2Cl_2 (c = 0.26 M); (3) Amberlyst 15, acetone, H_2O (v/v = 9:2, c = 0.14 M), 50 °C. [b]Yields in parentheses were determined using mesitylene as internal standard.

Table 5. Synthesis of 5-Substituted 1,3,4-Oxadiazolin-2-ones[a]

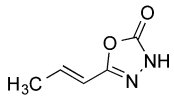




50: 84% (61%)[b]



51: 31%



52: 11%

[a]All yields refer to the one-pot protocol: (1) *tert*-butyl carbazate (1.05 equiv), Na_2SO_4 (3.10 equiv), $Cl(CH_2)_2Cl$ (c = 0.8 M), 85 °C; (2) Palau'chlor (2.00 equiv), 0 °C, 1 h, NEt_3 (3.30 equiv), 23 °C, CH_2Cl_2 (c = 0.26 M); (3) Amberlyst 15, acetone, H_2O (v/v = 9:2, c = 0.14 M), 50 °C. [b]NBS (1.05 equiv) was used instead of Palau'chlor.

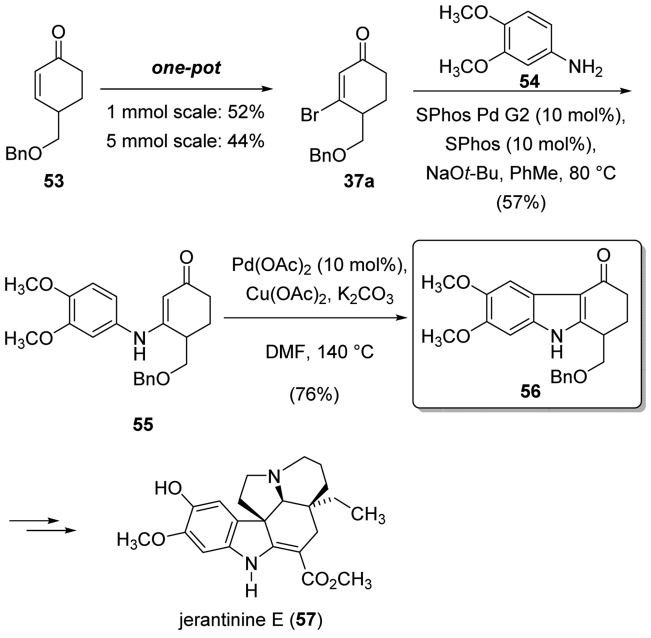
enone transposition sequence starting from β-ethoxy cyclohex-2-en-1-one.[28] The robustness of the one-pot protocol was then further demonstrated by performing the synthesis of β-bromo enone **37a** on a 5 mmol scale without significant decrease in yield. Palladium-catalyzed amination of **37a** with 3,4-dimethoxyaniline (**54**) proceeded in good yields using modified literature conditions.[29] Conversion of enaminone **55** to tetrahydrocarbazolone **56** was achieved by the oxidative Heck-type indole method developed by Glorius.[30] The route presented in Scheme 8 facilitates rapid diversification by simply exchanging the two coupling partners **37a** and **54**. Further studies toward the total synthesis of jerantinine E are currently under way in our laboratory.

■ CONCLUSION

For the first time, a one-pot protocol for the selective β-C−H bromination and chlorination of cyclic enones has been accomplished. The reaction proceeds by a three-step transformation using mild reaction conditions and features (1) umpolung of the enone by hydrazone formation, (2) selective β-C−H bromination with NBS or β-chlorination with

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

Scheme 8. Synthesis of the Tricyclic Jerantinine E Core



Palau'chlor to afford an intermediate allylic halogenide, and (3) hydrolysis of the hydrazone moiety.

Using these conditions, a broad range of cyclic enones could be converted to β-bromo and β-chloro enones. Crucial to the success of the chlorination reaction was the unique reaction profile of Palau'chlor. Further efforts are necessary to ultimately develop a catalytic process for the direct β-C−H bromination and chlorination of conjugated systems. The substrates for which halogenation remains a significant challenge are those bearing substituents at C6. Furthermore, we discovered that enals are converted to conjugated 5-substituted 1,3,4-oxadiazolinones under the experimental conditions. Finally, a short synthesis of the tetrahydrocarbazolone core structure of the *Aspidosperma* alkaloid jerantinine E was completed. The convergent route allows structural modifications prior to assembly of the tetrahydrocarbazolone fragment.

EXPERIMENTAL SECTION

General Methods. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed in flame-dried glassware under a positive pressure of argon. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC). The TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and exposure to either an aqueous solution of ceric ammoniummolybdate (CAM), an ethanolic solution of *para*-anisaldehyde (Anis), or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, CD_2Cl_2, or DMSO-d_6. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference. Infrared (IR) spectra were recorded on an FT-IR spectrometer. IR data is reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) or electron ionization (EI) using a sector field mass spectrometer. X-ray structural analyses were performed on a diffractometer using Mo Kα radiation (λ = 0.71073 Å, graphite monochromator).

Preparation of Conjugated Hydrazones. *Cyclohex-2-en-1-one N,N-Dimethylhydrazone (**17a**).* Scandium trifluoromethanesulfonate (0.01 M in acetonitrile, 0.21 mL, 2.07 μmol, 0.10 equiv) was transferred to a round-bottom flask, and the solvent was removed under reduced pressure at 25 °C. 2-(*tert*-Butyldimethylsilyl)-1,1-dimethylhydrazine (**58**; 468 mg, 2.69 mmol, 1.30 equiv) and cyclohex-2-en-1-one (0.20 mL, 2.07 mmol, 1 equiv) were added, and the reaction mixture was stirred at 130 °C. After 10 min, the reaction mixture was cooled to 23 °C with a water bath. The crude mixture was purified by flash column chromatography on silica gel (20% diethyl ether in dichloromethane) to afford **17a** as a slightly volatile light yellow oil (218 mg, 76%). The obtained characterization data were in full agreement with those values reported in the literature.[31]

*2-(tert-Butyldimethylsilyl)-1,1-dimethylhydrazine (**58**).* *tert*-Butyldimethylsilyl chloride (15.0 g, 99.5 mmol, 1 equiv) was placed in a pressure flask, and *N,N*-dimethylhydrazine (26.5 mL, 348 mmol, 3.50 equiv) was added dropwise. Upon completion of the addition, the reaction mixture was heated to 70 °C. After 3 h, the colorless solution was allowed to cool to 23 °C, upon which a colorless liquid phase separated from a white precipitate. The liquid phase was pipetted off, and residual *N,N*-dimethylhydrazine was removed by distillation on a rotary evaporator (150 mbar, 40 °C) to yield pure **58** as a colorless liquid (15.5 g, 89%). The compound could be stored at 6 °C under an argon atmosphere for a minimum of 2 months without any decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 6H), 0.89 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.0, 26.7, 17.8, −5.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (m), 2855 (m), 1462 (m), 1246 (m), 885 (vs), 829 (s), 776 (s) cm^{-1}. HR-MS (ESI): calcd for $(C_8H_{23}N_2Si)^+$ $(M + H)^+$: 175.1631, found: 175.1627.

*Benzhydrazone **17b**.* Benzhydrazide (639 mg, 4.70 mmol, 0.91 equiv) was added to a solution of cyclohex-2-en-1-one (0.50 mL, 5.16 mmol, 1 equiv) in ethanol (7 mL), and the resulting solution was heated to 80 °C. Two further portions of benzhydrazide (total 410 mg, 3.01 mmol, 0.58 equiv) were added to the solution after 1.5 and 3.5 h. After 22 h, the reaction mixture was concentrated, and the crude residue was purified by flash column chromatography on silica gel (2% methanol in dichloromethane) to afford **17b** (675 mg, 61%, dr = 5:1) as an off-white solid. **17b** major isomer: TLC (2% methanol in dichloromethane) R_f = 0.34 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 7.89−7.72 (m, 2H), 7.53−7.46 (m, 1H), 7.46−7.38 (m, 2H), 6.44−6.30 (m, 2H), 2.52−2.42 (t, J = 6.5 Hz, 2H), 2.23 (ddt, J = 6.3, 4.4, 2.7 Hz, 2H), 1.86 (app quin, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 154.3, 138.1, 133.8, 131.9, 128.8, 128.0, 127.4, 24.8, 23.9, 21.1. **17b** minor isomer: TLC (2% methanol in dichloromethane) R_f = 0.27 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (br s, 1H), 7.89−7.72 (m, 2H), 7.53−7.46 (m, 1H), 7.46−7.38 (m, 2H), 6.52−6.46 (m, 2H), 2.64−2.55 (m, 2H), 2.30 (app td, J = 6.1, 1.8 Hz, 2H), 1.86 (app quin, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 154.0, 143.5, 133.8, 131.8, 128.8, 127.3, 116.4, 31.7, 26.7, 22.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3216 (w), 2928 (w), 1645 (vs), 1519 (s), 1271 (s), 1131 (s), 910 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{14}N_2O_1)^+$ 214.1106, found 214.1101.

*tert-Butyl 2-(Cyclohex-2-en-1-ylidene)hydrazinecarboxylate (**17c**).* To a solution of cyclohex-2-en-1-one (678 μL, 7.00 mmol, 1 equiv) in 1,2-dichloroethane (4.7 mL) were added sodium sulfate (2.98 g, 21 mmol, 3.00 equiv) and *tert*-butyl carbazate (991 mg, 7.35 mmol, 1.35 equiv). The resulting suspension was heated to 85 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C. The suspension was diluted with dichloromethane (10 mL) and then was filtered. The filtrate was concentrated, and the desired product was obtained as a yellow solid. Slow crystallization (3 days) from hexanes/ethyl acetate at −25 °C afforded clear yellow crystals that were filtered off, washed with cold hexanes, and dried *in vacuo* to afford **17c** (1.40 g, 95%, dr = 4:1). TLC (dichloromethane): R_f = 0.20 (UV, Anis). **17c** major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.55 (br s, 1H), 6.25−6.12 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 2.12 (tdd, J = 5.8, 3.9, 1.5 Hz, 2H), 1.81−1.71 (m, 2H), 1.48−1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 149.7, 135.5, 127.9, 81.0, 28.2, 24.6, 23.4, 21.0. **17c** minor isomer, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.55 (br s, 1H), 6.36−6.29 (m, 2H), 2.46−2.39 (m, 2H), 2.19 (app td, J = 6.0, 1.6 Hz, 2H), 1.81−1.71 (m, 2H), 1.48−1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 148.6, 141.3, 116.3, 81.0, 31.5, 28.2, 26.4, 22.4.

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3237 (w), 2931 (w), 1713 (m), 1691 (m), 1238 (s), 1159 (vs), 1138 (s) cm^{-1}. HR-MS (EI): calcd for $(C_{11}H_{18}N_2O_2)^+$ 210.1368, found 210.1359.

*tert-Butyl 2-(3-Bromocyclohex-2-en-1-ylidene)hydrazine-1-carboxylate (**18c**).* Bromine (2 M solution in dichloromethane, 0.29 mL, 0.57 mmol, 1 equiv) was added dropwise to a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)hydrazinecarboxylate (**17c**; 120 mg, 0.57 mmol, 1 equiv, dr = 4:1) in dichloromethane (1.3 mL) at −15 °C. After 15 min, triethylamine (159 μL, 1.14 mmol, 2.00 equiv) was added in one portion, and the resulting dark brown slurry was allowed to warm to 23 °C. After 24 h, the reaction mixture was diluted with dichloromethane (10 mL), and the orange solution was washed with water (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 × 10 mL), the combined organic layers were dried over magnesium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the crude residue was purified by flash column chromatography on silica gel (100% dichloromethane) to afford **18c** as an orange oil (130 mg, 79%). TLC (100% dichloromethane): R_f = 0.43 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 6.65 (s, 1H), 2.60 (td, *J* = 6.2, 1.6 Hz, 2H), 2.29 (t, *J* = 6.7 Hz, 2H), 1.90 (app quin, *J* = 6.4 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 152.6, 148.5, 130.9, 130.3, 81.6, 35.0, 28.3, 22.2, 22.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3228 (w), 2978 (w), 1711 (m), 1695 (m), 1512 (m), 1235 (s), 1151 (vs) cm^{-1}. HR-MS (EI): calcd for $(C_{11}H_{17}N_2O_2{}^{79}Br)^+$ 288.0473, found 288.0450.

*(Z)-tert-Butyl 2-(3-Bromocyclohex-1-en-1-yl)diazenecarboxylate (**22**).* To a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)-hydrazinecarboxylate (**17c**; 21.0 mg, 0.10 mmol, 1 equiv, dr = 4:1) in dichloromethane (0.5 mL) was added freshly recrystallized *N*-bromosuccinimide (19.6 mg, 0.11 mmol, 1.10 equiv) in one portion at 0 °C. After 1 h, the reaction mixture was allowed to warm to 23 °C. The orange solution was diluted with dichloromethane (5 mL) and then was concentrated. The residual dark red oil was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **22** as an orange oil (25 mg, 86%). Crystals that were suitable for X-ray analysis could be obtained by crystallization from hexanes at −25 °C. TLC (25% ethyl acetate in hexanes): R_f = 0.81 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (ddt, *J* = 5.0, 2.0, 0.9 Hz, 1H), 5.12 (tdd, *J* = 4.1, 2.9, 1.1 Hz, 1H), 2.56−2.45 (m, 1H), 2.29−2.17 (m, 2H), 2.16−1.94 (m, 2H), 1.85 (dddd, *J* = 9.8, 8.9, 3.9, 1.8 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 155.1, 144.4, 85.0, 46.2, 32.2, 27.9, 21.4, 17.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (w), 1747 (s), 1477 (w), 1370 (m), 1270 (m), 1251 (s), 1133 (vs) cm^{-1}. HR-MS (ESI): calcd for $(C_{11}H_{16}N_2O_2{}^{79}Br)^+$ $(M - H)^+$ 287.0390, found 287.0397.

*1,3-Diiodocyclohex-1-ene (**27**).* To a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)hydrazinecarboxylate (**17c**; 21.0 mg, 0.10 mmol, 1 equiv, dr = 4:1) in dichloromethane (0.5 mL) was added *N*-iodosuccinimide (26.1 mg, 0.11 mmol, 1.10 equiv) in one portion at 25 °C. The flask then was covered with aluminum foil. After 4 h, the solution was concentrated, and the residual dark red oil was purified by flash column chromatography on silica gel (9% to 25% ethyl acetate in hexanes) to afford **27** as a yellow oil (8 mg, 24%), which was found to be unstable upon exposure to light. TLC (25% ethyl acetate in hexanes): R_f = 0.89 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (dd, *J* = 4.9, 2.3 Hz, 1H), 5.03−5.96 (m, 1H), 2.87−2.79 (m, 2H), 2.26−2.07 (m, 2H), 1.89−1.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 100.6, 39.1, 32.3, 29.0, 22.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2926 (m), 1613 (m), 1433 (w), 1422 (w), 1310(m), 1249 (w), 1161 (s) cm^{-1}.

*(Z)-tert-Butyl 2-(3-Chlorocyclohex-1-en-1-yl)diazene-1-carboxylate (**24**).* To a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)-hydrazinecarboxylate (**17c**; 105 mg, 0.50 mmol, 1 equiv) in dichloromethane (2.5 mL) was added Palau'chlor (210 mg, 1.00 mmol, 2.00 equiv) in one portion at 0 °C. After 1 h, the reaction mixture was allowed to warm to 23 °C. The orange suspension was filtered through a short plug of Celite, and the filtrate was concentrated. The residual oil was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **24** as an orange oil (77 mg, 63%). TLC (33% ethyl acetate in hexanes): R_f = 0.81 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (dddd, *J* = 4.5, 1.8, 1.3, 0.6 Hz, 1H), 4.95−4.90 (m, 1H), 2.44−2.33 (m, 1H), 2.22−2.06 (m, 3H), 2.06−1.92 (m, 1H), 1.83−1.73 (m, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 155.8, 143.6, 85.0, 54.2, 32.1, 28.0, 21.4, 18.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3248 (w), 2978 (w), 2360 (w), 1733 (s), 1507 (w), 1369 (m), 1250 (m), 1155 (vs) cm^{-1}. HR-MS (EI): calcd for $(C_{11}H_{17}O_2N_2{}^{35}Cl)^+$ 244.0979, found 244.0966.

*(Z)-tert-Butyl 2-(3-Fluorocyclohex-1-en-1-yl)diazenecarboxylate (**29**).* To a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)-hydrazinecarboxylate (**17c**; 105 mg, 0.5 mmol, 1 equiv, dr = 4:1) in acetonitrile (2 mL) was added Selectfluor (**28**; 196 mg, 0.53 mmol, 1.05 equiv) in one portion at 23 °C. After 3 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (2 mL) and stirring was continued for 10 min before diethyl ether (5 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 5 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the residual yellow oil was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to afford **29** as a yellow oil (2 mg, 2%). TLC (20% ethyl acetate in hexanes): R_f = 0.67 (UV, Anis). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17−7.06 (m, 1H), 5.49−5.18 (m, 1H), 2.42−2.24 (m, 1H), 2.23−2.11 (m, 1H), 2.08−1.85 (m, 3H), 1.62 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.7, 157.4 (d, *J* = 13.3 Hz), 141.0 (d, *J* = 19.9 Hz), 87.0 (d, *J* = 166.4 Hz), 85.9, 29.1 (d, *J* = 20.4 Hz), 28.0, 21.6, 17.8 (d, *J* = 7.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −172.55 to −173.05 (m).

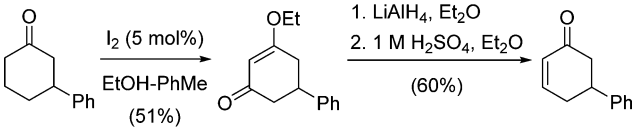
*tert-Butyl 2-(3-(Trifluoromethyl)cyclohex-2-en-1-ylidene)-hydrazine-1-carboxylate (**59**).* To a solution of *tert*-butyl 2-(cyclohex-2-en-1-ylidene)hydrazinecarboxylate (**17c**; 21.0 mg, 0.10 mmol, 1 equiv, dr = 4:1) in degassed dichloromethane (1 mL) were added 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (41.3 mg, 0.13 mmol, 1.25 equiv) and copper(I) chloride (1 mg, 0.01 mmol, 0.10 equiv), and the reaction mixture was heated to 45 °C. After 43 h, the reaction mixture was allowed to cool to 23 °C. The brown solution was diluted with ethyl acetate (5 mL) and then filtered through a short plug of Celite. The filter cake was washed with ethyl acetate (70 mL). The filtrate was concentrated, and the residual brown oil was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **59** as a crystalline white solid (13.5 mg, 49%). TLC (25% ethyl acetate in hexanes): R_f = 0.47 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 6.79 (app q, *J* = 1.7 Hz, 1H), 2.37−2.29 (m, 4H), 1.97−1.88 (m, 2H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.3, 146.6, 133.5 (q, *J* = 31.3 Hz), 129.2 (q, *J* = 6.1 Hz), 123.6 (q, *J* = 271.5 Hz), 82.1, 28.4, 22.8, 22.1 (d, *J* = 1.6 Hz), 20.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3221, 2981, 1714, 1520, 1368, 1302, 1241, 1151, 1115 cm^{-1}. HR-MS (EI): calcd for $(C_{12}H_{17}F_3N_2O_2)^+$ 278.1242, found 278.1239.

Preparation of Enones. Cyclohex-2-en-1-one, 4,4-dimethylcyclohex-2-en-1-one, 4-methyl-4-phenylcyclohex-2-en-1-one, 4,4-diphenylcyclohex-2-en-1-one, and cyclohept-2-en-1-one are commercially available and were used without further purification. Methyl 1-methyl-4-oxo-2-cyclohexene-1-carboxylate,[32] (*R*)-4-hydroxycyclohex-2-en-1-one,[33] 4-[(phenylmethoxy)methyl]-2-cyclohex-2-en-1-one,[28] 4-(trifluoromethyl)cyclohex-2-en-1-one,[34] 4-(prop-2-yn-1-yl)cyclohex-2-en-1-one,[35] 5,5-dimethylcyclohex-2-en-1-one,[36] 5-oxo-3-cyclohexene-1-acetonitrile,[37] and 6-methylcyclohex-2-en-1-one[38] were prepared according to known literature procedures.

*3-Ethoxy-5-phenylcyclohex-2-en-1-one (**60**).* To a solution of 5-phenyl-1,3-cyclohexanedione (1.88 g, 10.0 mmol, 1 equiv) in ethanol−toluene (v/v = 10:1, 22 mL) was added iodine (127 mg, 0.50 mmol, 0.05 equiv), and the dark red solution was stirred at 23 °C. After 16 h, the mixture was concentrated, the residual dark red oil was dissolved in diethyl ether (20 mL), and the solution was washed with saturated aqueous sodium thiosulfate solution (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (20

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

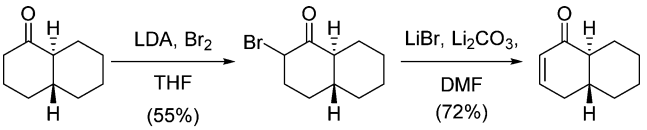
mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **60** as a yellow oil (1.1 g, 51%). TLC (33% ethyl acetate in hexanes): R_f = 0.19 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, C_6D_6): δ 7.12−7.00 (m, 3H), 6.90−6.84 (m, 2H), 5.40 (s, 1H), 3.33−3.17 (m, 2H), 3.01−2.86 (m, 1H), 2.60 (dd, J = 16.2, 4.6 Hz, 1H), 2.35 (dd, J = 16.1, 12.7 Hz, 1H), 2.27−2.23 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 196.4, 175.3, 143.5, 128.9, 127.0, 127.0, 103.0, 64.0, 44.3, 39.5, 36.7, 14.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2979 (w), 1650 (s), 1596 (s), 1497 (w), 1453 (w), 1402 (w), 1376 (s), 1347 (m), 1204 (s), 1137 (m), 1110 (m), 1025 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{14}H_{16}O_2)^+$ 216.1150, found 216.1149.



60 61

5-Phenylcyclohex-2-en-1-one (**61**). A solution of 3-ethoxy-5-phenylcyclohex-2-en-1-one (**60**; 1.00 g, 4.62 mmol, 1 equiv) in diethyl ether (3.75 mL) was added dropwise to a suspension of lithium aluminum hydride (175 mg, 4.62 mmol, 1 equiv) in diethyl ether (15 mL) at 0 °C over a period of 5 min. The reaction mixture was allowed to warm to 23 °C. After 1 h, water (20 mL) followed by 1 M hydrochloric acid (10 mL) was carefully added. The aqueous layer was extracted with diethyl ether (3 × 30 mL), the combined organic layers were washed with saturated aqueous potassium carbonate solution and saturated aqueous sodium chloride solution (20 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residual oil was dissolved in diethyl ether (50 mL), and water (5 mL) followed by 1 M sulfuric acid (10 mL) was added. The reaction mixture was stirred at 23 °C for 1 h. The layers were separated, and the organic layer was washed with saturated aqueous potassium carbonate solution (20 mL) and saturated aqueous sodium chloride solution (20 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **61** as a yellow oil (480 mg, 60%). The obtained characterization data were in full agreement with those values reported in the literature.[34]

2-Bromooctahydro-1(2H)-naphthalenone (**62**). A solution of diisopropylamine (1.10 mL, 7.80 mmol, 1.30 equiv) in tetrahydrofuran (27 mL) was cooled to −78 °C. *n*-Butyllithium (2.5 M in hexanes, 2.88 mL, 7.20 mmol, 1.20 equiv) was added, and the solution was warmed to 0 °C. After 10 min, the mixture was cooled to −78 °C, and a solution of *trans*-1-decalone (932 mg, 6.00 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, bromine (369 μL, 7.20 mmol, 1.20 equiv) was added dropwise. The solution was stirred for 5 min and then was poured onto 0.5 N hydrochloric acid (100 mL) at 23 °C. The aqueous layer was extracted with dichloromethane (3 × 40 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL), and the washed organic solution was dried over magnesium sulfate. The dried solution was filtered, the filtrate was concentrated, and the residual orange oil was purified by flash column chromatography on silica gel (4% diethyl ether in pentane) to afford a mixture of **62***α* (colorless solid) and **62***β* (colorless oil) (758 mg, 55%, α/β = 3:4). **62***α*, TLC (17% ethyl acetate in hexanes): R_f = 0.80 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (ddd, J = 13.3, 6.1, 1.3 Hz, 1H), 2.70−2.57 (m, 1H), 2.17−2.01 (m, 2H), 1.98−1.90 (m, 1H), 1.88−1.77 (m, 3H), 1.76−1.69 (m, 1H), 1.63−1.50 (m, 1H), 1.50−1.31 (m, 2H), 1.27−1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 51.9, 48.7, 44.8, 34.6, 34.1, 27.7, 25.7, 25.4, 25.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2918 (m), 2845 (m), 1719 (s), 1445 (m), 1305 (m), 1285 (m), 1162 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{10}H_{15}O^{79}Br)^+$ 230.0306, found 230.0305. **62***β*, TLC (17% ethyl acetate in hexanes): R_f = 0.72 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36−4.29 (m, 1H), 2.93−2.76 (m, 1H), 2.30−2.22 (m, 1H), 2.21−2.09 (m, 1H), 1.96−1.83 (m, 2H), 1.83−1.74 (m, 2H), 1.74−1.66 (m, 1H), 1.65−1.56 (m, 1H), 1.43−1.31 (m, 1H), 1.29−1.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 56.9, 54.5, 44.9, 39.1, 34.1, 34.0, 25.8, 25.5, 25.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2916 (m), 2916 (m), 2852 (m), 1708 (s), 1446 (s), 1428 (m), 1367 (m), 1348 (m), 1303 (m), 1197 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{10}H_{15}O^{79}Br)^+$ 230.0306, found 230.0292.



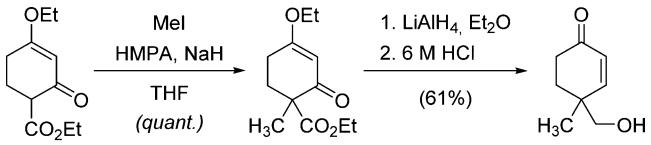
62 63

(4aS,8aR)-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (**63**). Lithium bromide (260 mg, 3.00 mmol, 1.50 equiv) and lithium carbonate (369 mg, 5.00 mmol, 2.50 equiv) were suspended in *N*,*N*-dimethylformamide (3.5 mL), and the mixture was stirred for 2 min before a solution of 2-bromooctahydro-1(2*H*)-naphthalenone (**62**; 462 mg, 2.00 mmol, 1 equiv, α/β = 1:1) in tetrahydrofuran (6.8 mL) was added. The milky suspension was heated to 120 °C. After 5 h, the mixture was allowed to cool to 23 °C and then was diluted with 5% acetic acid in water (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL), the combined organic layers were washed with water (3 × 10 mL) and saturated aqueous sodium chloride solution (10 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the residual orange oil was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **63** as a white solid (217 mg, 72%). TLC (25% ethyl acetate in hexanes): R_f = 0.63 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (ddd, J = 10.1, 5.9, 2.2 Hz, 1H), 5.95 (ddd, J = 10.0, 3.1, 0.9 Hz, 1H), 2.32 (dddd, J = 18.7, 5.6, 4.3, 0.9 Hz, 1H), 2.27−2.19 (m, 1H), 2.14−2.03 (m, 1H), 2.00−1.89 (m, 1H), 1.86−1.64 (m, 4H), 1.31−1.03 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 149.0, 129.6, 51.1, 40.1, 33.8, 33.7, 25.7, 25.6, 25.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2918 (m), 2852 (m), 1664 (s), 1446 (w), 1422 (w), 1388 (w), 1302 (w), 1244 (w), 1207 (w), 1177 (w) cm^{-1}. HR-MS (EI): calcd for $(C_{10}H_{14}O)^+$ 150.1045, found 150.1033.

4-(Hydroxymethyl)-4-methylcyclohex-2-en-1-one (**65**). Ethyl 4-ethoxy-2-oxocyclohex-3-enecarboxylate[39] (2.00 g, 9.42 mmol, 1.00 equiv) was dissolved in tetrahydrofuran (28 mL), and the resulting solution was cooled to 0 °C. Sodium hydride (452 mg, 11.3 mmol, 1.20 equiv, 60 wt % dispersion in mineral oil) was added in two portions, and the resulting suspension was stirred for 45 min at 0 °C. Hexamethylphosphoramide (2.70 g, 15.1 mmol, 1.60 equiv) and iodomethane (704 μL, 11.3 mmol, 1.20 equiv) were then added, and the reaction mixture was warmed to 23 °C. After 3.5 h, saturated aqueous ammonium chloride solution (25 mL) and ethyl acetate (20 mL) were added. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (2 × 30 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford **64** (2.40 g, quantitative), which was used in the next reaction without further purification. The crude product was dissolved in diethyl ether (8 mL), and the so-obtained solution was added dropwise to a solution of lithium aluminum hydride (393 mg, 10.4 mmol, 1.10 equiv) in diethyl ether (33 mL) at 0 °C. The reaction mixture was warmed to 23 °C, and stirring was continued for 3 h before the reaction mixture was cooled to 0 °C and was carefully diluted with water (2 mL), followed by 6 M hydrochloric acid (15 mL). The resulting suspension was stirred at 23 °C for 20 min and then was diluted with diethyl ether (10 mL). The layers were separated, the organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL), water (20 mL), and saturated aqueous sodium chloride solution (30 mL), and the washed solution was dried over sodium sulfate. The dried solution

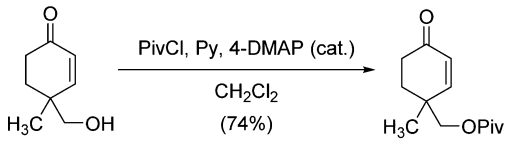
DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

was filtered, the filtrate was concentrated, and the residual yellow oil was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **65** as a colorless oil (805 mg, 61%). The obtained characterization data were in full agreement with values previously reported.[40]



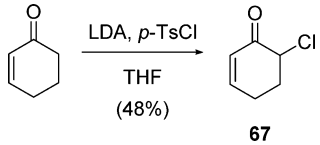
64 **65**

*(1-Methyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (**66**).* To a solution of 4-(hydroxymethyl)-4-methyl-2-cyclohexen-1-one (**65**; 650 mg, 4.64 mmol, 1 equiv) in dichloromethane (9 mL) were added pyridine (1.50 mL, 18.5 mmol, 4.00 equiv) and 4-dimethylaminopyridine (28.3 mg, 0.23 mmol, 0.05 equiv) at 0 °C. Pivaloyl chloride (1.14 mL, 9.27 mmol, 2.00 equiv) was added dropwise within 10 min. The solution was stirred for 16 h at 23 °C before water (10 mL) and ethyl acetate (10 mL) were added. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the residual colorless oil was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to afford **66** as a colorless oil (770 mg, 74%). TLC (17% ethyl acetate in hexanes): R_f = 0.45 (CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (ddt, J = 10.3, 2.9, 1.2 Hz, 1H), 5.97 (ddd, J = 10.3, 4.0, 1.7 Hz, 1H), 4.11−4.04 (m, 1H), 3.93−3.86 (m, 1H), 2.56−2.44 (m, 2H), 2.12−2.01 (m, 1H), 1.88−1.76 (m, 1H), 1.22−1.17 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 178.3, 154.5, 129.3, 70.2, 39.1, 36.9, 34.0, 31.6, 27.3, 22.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (w), 1727 (s), 1681 (s), 1480 (m), 1460 (m), 1391 (w), 1377 (w), 1280 (m), 1146 (s) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{20}O_3)^+$ 224.1412, found 224.1399.



65 **66**

*6-Chlorocyclohex-2-en-1-one (**67**).* To a solution of diisopropylamine (1.36 mL, 9.6 mmol, 1.20 equiv) in tetrahydrofuran (8 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 3.52 mL, 8.80 mmol, 1.10 equiv) at −78 °C, and stirring was continued for 10 min before the solution was warmed to 0 °C over 20 min. The solution was then cooled to −78 °C and a solution of cyclohex-2-en-1-one (0.77 mL, 8.00 mmol, 1 equiv) in tetrahydrofuran (16 mL) was added dropwise over 10 min. After 45 min, a solution of *p*-toluenesulfonyl chloride (1.60 g, 8.40 mmol, 1.05 equiv) in tetrahydrofuran (16 mL) was added dropwise over 10 min. The yellow solution was warmed to 23 °C and stirring was continued for 1 h. Saturated aqueous ammonium chloride solution (30 mL) and diethyl ether (20 mL) were added. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **67** (496 mg, 48%) as a colorless oil. TLC (17% ethyl acetate in hexanes): R_f = 0.34 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01 (dt, J = 9.8, 4.0 Hz, 1H), 6.08 (dt, J = 10.1, 1.9 Hz, 1H), 4.41 (dd, J = 7.8, 3.8 Hz, 1H), 2.69−2.60 (m, 1H), 2.49−2.39 (m, 2H), 2.37−2.29 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.7, 150.7, 127.7, 59.1, 32.2, 23.8. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930 (w), 1681 (s), 1615 (w), 1418 (w), 1391 (m), 1383 (m), 1219 (m), 1121 (m) cm^{-1}. HR-MS (EI): calcd for $(C_6H_7O^{35}Cl)^+$ 130.0185, found 130.0189.



67

The One-Pot β-C−H Halogenation of Enones. *General Experimental Procedures for Compounds **20a, 31a−35a, 36, 37a, 38, 39a, 40−42, 43a−45a, and 46**.* The enone (1.00 mmol, 1 equiv) was added to a mixture of sodium sulfate (440 mg, 3.10 mmol, 3.10 equiv) and *tert*-butyl carbazate (142 mg, 1.05 mmol, 1.05 equiv) in 1,2-dichloroethane (0.8 mL) in a pressure flask. The resulting suspension was heated to 85 °C. After 4.5 h, the reaction mixture was allowed to cool to 23 °C. Dichloromethane (3 mL) was added, the solution was cooled to 0 °C, and recrystallized *N*-bromosuccinimide (187 mg, 1.05 mmol, 1.05 equiv) was added. After 1 h, triethylamine (292 μL, 2.10 mmol, 2.10 equiv) was added in one portion. The resulting suspension was allowed to warm to 23 °C and was stirred at 23 °C until full consumption of the intermediate allylic bromide (monitored by TLC) was observed. Acetone−water (v/v = 9:2, 3.5 mL) and Amberlyst 15 (1.20 g) were added, and the suspension was heated to 50 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and then was diluted with dichloromethane (4 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes or diethyl ether/pentane) to afford the product.

*3-Bromocyclohex-2-en-1-one (**20a**).* The general procedure was followed, using cyclohex-2-en-1-one (96.1 mg, 1.00 mmol), affording **20a** after purification by flash column chromatography (9% ethyl acetate in hexane) as a colorless oil (97 mg, 55%). The obtained characterization data were in full agreement with those previously reported.[11a]

*3-Bromo-4,4-dimethylcyclohex-2-en-1-one (**31a**).* The general procedure was followed, using 4,4-dimethylcyclohex-2-en-1-one (124 mg, 1.00 mmol), affording **31a** after purification by flash column chromatography (8% ethyl acetate in hexane) as a colorless oil (139 mg, 68%). TLC (dichloromethane): R_f = 0.35 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 1H), 2.53−2.41 (m, 2H), 2.08−1.93 (m, 2H), 1.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 162.6, 132.1, 39.6, 36.2, 34.3, 27.8. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (w), 1678 (vs), 1583 (m), 1294 (m), 1265 (m), 953 (m), 942 (m) cm^{-1}. HR-MS (ESI): calcd for $(C_8H_{12}O^{79}Br)^+$ (M + H)$^+$ 203.0066, found 203.0067.

*3-Bromo-4-methyl-4-phenylcyclohex-2-en-1-one (**32a**).* The general procedure was followed, using 4-methyl-4-phenylcyclohex-2-en-1-one (167 mg, 0.90 mmol), affording **32a** after purification by flash column chromatography (8% ethyl acetate in hexanes) as a colorless solid (167 mg, 70%). TLC (25% ethyl acetate in hexanes): R_f = 0.67 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.23 (m, 5H), 6.71 (s, 1H), 2.43−2.21 (m, 4H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 159.1, 142.8, 134.5, 128.8, 127.4, 126.5, 47.9, 39.2, 34.2, 27.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (w), 1673 (vs), 1597 (m), 1585 (m), 1443 (m), 1280 (m), 1203 (m), 950 (s) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{13}O^{79}Br)^+$ 264.0150, found 264.0131.

*3-Bromo-4,4-diphenylcyclohex-2-en-1-one (**33a**).* The general procedure was followed, using 4,4-diphenylcyclohex-2-en-1-one (248 mg, 1.00 mmol), affording **33a** after purification by flash column chromatography (9% ethyl acetate in hexanes) as an off-white crystalline solid (206 mg, 63%). TLC (25% ethyl acetate in hexanes): R_f = 0.59 (UV, Anis). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.48−7.22 (m, 10H), 6.80 (s, 1H), 2.96−2.78 (m, 2H), 2.38−2.04 (m, 2H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 195.8, 157.7, 143.1, 135.8, 129.6, 128.8, 128.0, 58.2, 39.4, 35.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2945 (w), 1667 (s), 1577 (m), 1494 (m), 1279 (m), 1212 (m), 1173 (m), 970 (m), 940 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{18}H_{15}O^{79}Br)^+$ 326.0306, found 326.0310.

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

*Methyl 2-Bromo-1-methyl-4-oxo-2-cyclohexene-1-carboxylate (**34a**).* The general procedure was followed, using methyl 1-methyl-4-oxo-2-cyclohexene-1-carboxylate (168 mg, 1.00 mmol), affording **34a** after purification by flash column chromatography (6% ethyl acetate in hexanes) as a colorless oil (172 mg, 70%). TLC (25% ethyl acetate in hexanes): R_f = 0.53 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 1H), 3.78 (s, 3H), 2.59−2.41 (m, 3H), 2.14−2.04 (m, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 172.9, 152.3, 133.9, 53.2, 51.1, 34.0, 24.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (w), 1733 (s), 1681 (s), 1602 (w), 1456 (w), 1291 (m), 1267 (m), 1251 (s), 1173 (s), 1115 (m) cm^{-1}. HR-MS (EI): calcd for $(C_9H_{11}O_3{}^{79}Br)^+$ 245.9892, found 245.9866.

*(2-Bromo-1-methyl-4-oxocyclohex-2-en-1-yl)methyl Pivalate (**35a**).* The general procedure was followed, using (1-methyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (**66**; 224 mg, 1.00 mmol), affording **35a** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a colorless oil (178 mg, 59%). TLC (12.5% ethyl acetate in hexanes): R_f = 0.29 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 4.30 (d, J = 11.2 Hz, 1H), 3.92 (d, J = 11.2 Hz, 1H), 2.57−2.50 (m, 2H), 2.30 (ddd, J = 13.7, 9.7, 6.1 Hz, 1H), 1.95 (ddd, J = 13.7, 6.4, 5.3 Hz, 1H), 1.29 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 178.1, 157.0, 134.3, 69.8, 42.9, 39.0, 33.8, 31.7, 27.2, 22.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (w), 2934 (w), 1729 (s), 1681 (s), 1596 (m), 1479 (m), 1460 (m), 1208 (s), 1188 (w), 1141 (s) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{20}O_3{}^{79}Br)^+$ $(M + H)^+$ 303.0596, found 303.0580.

*(R)-3-Bromo-4-hydroxycyclohex-2-en-1-one (**36**).* The general procedure was followed, using (*R*)-4-hydroxycyclohex-2-en-1-one (112 mg, 1.00 mmol), affording **36** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a yellow oil (52 mg, 27%). TLC (75% ethyl acetate in hexane): R_f = 0.65 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 1H), 4.54 (t, J = 5.8 Hz, 1H), 2.94 (s, 1H), 2.66 (ddd, J = 17.7, 8.1, 4.7 Hz, 1H), 2.40 (dddd, J = 17.9, 12.4, 9.3, 4.7 Hz, 2H), 2.19−2.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 152.7, 132.9, 70.0, 34.0, 30.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3400 (br), 2932 (w), 1668 (s), 1590 (m), 1443 (w), 1326 (w), 1284 (m), 1193 (m) cm^{-1}. HR-MS (EI): calcd for $(C_6H_7O_2{}^{79}Br)^+$ 189.9629, found 189.9616. $[\alpha]_D{}^{25}$ = −26.9° (*c* = 1.89 M, CH_2Cl_2).

*4-((Benzyloxy)methyl)-3-bromocyclohex-2-en-1-one (**37a**).* The general procedure was followed, using 4-[(phenylmethoxy)methyl]-2-cyclohex-2-en-1-one (216 mg, 1.00 mmol), affording **37a** after purification by flash column chromatography (14% ethyl acetate in hexanes) as a yellow oil (154 mg, 52%). TLC (25% ethyl acetate in hexanes): R_f = 0.58 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 5H), 6.52 (d, J = 1.2 Hz, 1H), 4.63−4.49 (m, 2H), 3.79−3.70 (m, 2H), 2.97−2.90 (m, 1H), 2.56 (ddd, J = 17.0, 10.0, 6.1 Hz, 1H), 2.36 (dt, J = 17.1, 5.6 Hz, 1H), 2.29−2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 151.2, 137.8, 134.3, 128.6, 127.9, 127.7, 73.4, 70.3, 44.5, 34.2, 25.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2862 (w), 1678 (s), 1605 (m), 1452 (w), 1363 (w), 1329 (w), 1277 (w), 1234 (w), 1101 (m) cm^{-1}. HR-MS (ESI): calcd for $(C_{14}H_{16}O_2{}^{79}Br)^+$ $(M + H)^+$ 295.0334, found 295.0327.

*3-Bromo-4-(trifluoromethyl)cyclohex-2-en-1-one (**38**).* The general procedure was followed, using 4-(trifluoromethyl)cyclohex-2-en-1-one (164 mg, 0.96 mmol), affording **38** after purification by flash column chromatography (17% diethyl ether in pentane) as a volatile yellow oil (120 mg, 52%). TLC (20% diethyl ether in pentane): R_f = 0.38 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 1H), 3.47 (qdd, J = 8.4, 5.7, 2.8 Hz, 1H), 2.68−2.54 (m, 1H), 2.53−2.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 139.5 (q, J = 1.6 Hz), 137.3, 125.5 (q, J = 283.0 Hz), 47.6 (q, J = 27.8 Hz), 32.5, 23.3 (q, J = 2.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.85 (dq, J = 8.5, 1.4 Hz). IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2946 (w), 1689 (s), 1611 (m), 1367 (m), 1327 (m), 1259 (m), 1237 (m), 1189 (s), 1155 (s), 1118 (s) cm^{-1}. HR-MS (EI): calcd for $(C_7H_6O^{79}BrF_3)^+$ 241.9554, found 241.9554.

*3-Bromo-4-(prop-2-yn-1-yl)cyclohex-2-en-1-one (**39a**).* The general procedure was followed, using 4-(prop-2-yn-1-yl)cyclohex-2-en-1-one (172 mg, 1.00 mmol), affording **39a** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a yellow oil (100 mg, 47%). TLC (20% ethyl acetates in hexanes): R_f = 0.61 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, J = 1.3 Hz, 1H), 2.90 (dddd, J = 9.1, 5.3, 3.8, 1.4 Hz, 1H), 2.76 (ddd, J = 17.0, 3.7, 2.7 Hz, 1H), 2.64−2.52 (m, 2H), 2.42 (ddd, J = 17.1, 7.6, 4.9 Hz, 1H), 2.37−2.20 (m, 2H), 2.08 (t, J = 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 152.6, 133.9, 80.6, 71.5, 42.8, 34.2, 26.7, 22.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3292 (m), 1676 (s), 1605 (m), 1329 (m), 1283 (m), 1237 (m), 1148 (m) cm^{-1}. HR-MS (EI): calcd for $(C_9H_8O^{79}Br)^+$ $(M - H)^+$ 210.9759, found 210.9740.

*3-Bromo-5,5-dimethlycyclohex-2-en-1-one (**40**).* The general procedure was followed, using 5,5-dimethlycyclohex-2-en-1-one (119 mg, 0.96 mmol), affording **40** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a yellowish oil (75 mg, 39%). The obtained characterization data were in full agreement with those previously reported.[11a]

*3-Bromo-5-oxo-3-cyclohexene-1-acetonitrile (**41**).* The general procedure was followed, using 5-oxo-3-cyclohexene-1-acetonitrile (84 mg, 0.62 mmol), affording **41** after purification by flash column chromatography (33% ethyl acetate in hexanes) as a yellow oil (41 mg, 31%). TLC (33% ethyl acetates in hexanes): R_f = 0.28 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (d, J = 2.4 Hz, 1H), 3.05−2.96 (m, 1H), 2.73−2.85 (m, 1H), 2.68−2.56 (m, 2H), 2.53−2.57 (m, 2H), 2.37−2.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 147.4, 132.6, 116.8, 41.6, 41.1, 32.2, 22.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2922 (w), 2251 (m), 1680 (s), 1606 (s), 1427 (m), 1370 (w), 1327 (w), 1283 (m), 1237 (m) cm^{-1}. HR-MS (EI): calcd for $(C_8H_8NO^{79}Br)^+$ 212.9789, found 212.9776.

*(S)-3-Bromo-5-isopropyl-2-methylcyclohex-2-en-1-one (**42**).* The general procedure was followed, using (−)-carvotanacetone (152 mg, 1.00 mmol), affording **42** after purification by flash column chromatography (5% ethyl acetate in hexanes) as a yellow oil (76 mg, 33%). TLC (dichloromethane): R_f = 0.73 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (ddt, J = 18.1, 4.8, 1.5 Hz, 1H), 2.74−2.62 (m, 1H), 2.57 (ddd, J = 15.9, 3.7, 1.5 Hz, 1H), 2.15 (dd, J = 15.9, 13.5 Hz, 1H), 1.94 (dd, J = 2.5, 1.4 Hz, 3H), 1.64−1.53 (m, 1H), 0.93 (dd, J = 6.8, 3.4 Hz, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 147.2, 136.2, 41.8, 41.6, 41.4, 31.9, 19.6, 15.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (m), 2874 (w), 1677 (vs), 1627 (m), 1328 (w), 1288 (s), 970 (w) cm^{-1}. HR-MS (ESI): calcd for $(C_{10}H_{16}OBr)^+$ $(M + H)^+$ 231.0380, found 231.0380. Optical rotation $[\alpha]_D{}^{23}$ = −87.8 (*c* = 0.51, CH_2Cl_2).

*3-Bromo-5-phenylcyclohex-2-en-1-one (**43a**).* The general procedure was followed, using 5-phenylcyclohex-2-en-1-one (**61**; 172 mg, 1.00 mmol), affording **43a** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a yellow oil (112 mg, 45%). TLC (25% ethyl acetates in hexanes): R_f = 0.80 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.39−7.33 (m, 2H), 7.31−7.23 (m, 3H), 6.55−6.53 (m, 1H), 3.46 (ddt, J = 11.4, 9.8, 5.9 Hz, 1H), 3.08−3.01 (m, 2H), 2.67−2.61 (m, 2H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 195.8, 149.3, 142.4, 132.8, 129.4, 127.8, 127.2, 44.4, 43.8, 41.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3061 (w), 3025 (w), 1673 (s), 1603 (s), 1495 (m), 1453 (m), 1422 (m), 1367 (m), 1331 (m), 1275 (s), 1232 (s), 1137 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{12}H_{11}O^{79}Br)^+$ 249.9993, found 249.9968.

*3-Bromo-6-methlycyclohex-2-en-1-one (**44a**).* The general procedure was followed, using 6-methylcyclohex-2-en-1-one (116 mg, 1.00 mmol), affording **44a** after purification by flash column chromatography as a colorless oil (65 mg, 34%). TLC (25% ethyl acetate in hexanes): R_f = 0.63 (UV, Anis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (dd, J = 2.2, 1.0 Hz, 1H), 2.96−2.73 (m, 2H), 2.42−2.31 (m, 1H), 2.14−2.05 (m, 1H), 1.88−1.75 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 149.1, 132.1, 40.4, 36.2, 31.2, 14.8. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2931 (w), 1673 (s), 1607 (m), 1338 (m), 1190 (m) cm^{-1}. HR-MS (EI): calcd for $(C_7H_9O^{81}Br)^+$ 189.9816, found 189.9815.

*3-Bromo-2-cyclohepten-1-one (**45a**).* The general procedure was followed, using 2-cyclohepten-1-one (115 mg, 1.00 mmol), affording **45a** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a yellow oil (53 mg, 28%) that contained minor

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

impurities. The obtained characterization data were in full agreement with those previously reported.[41]

*3-Bromo-2-phenyl-2-cyclopenten-1-one (**46**).* The general procedure was followed, using 2-phenyl-2-cyclopenten-1-one (110 mg, 0.70 mmol), affording **46** after purification by flash column chromatography (9% ethyl acetate in hexanes) as a colorless oil (71 mg, 43%). TLC (50% ethyl acetate in hexanes): R_f = 0.76 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.53−7.35 (m, 5H), 3.12−3.05 (m, 2H), 2.71−2.64 (m, 2H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 202.5, 156.5, 143.5, 130.9, 129.5, 129.1, 128.6, 36.9, 36.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3052 (w), 2923 (w), 1701 (s), 1622 (w), 1492 (m), 1283 (m), 1270 (m), 1152 (s) cm^{-1}. HR-MS (ESI): calcd for $(C_{11}H_{10}O^{79}Br)^+$ (M + H)$^+$ 236.9915, found 236.9909.

*General Experimental Procedures for Compounds **20b**, **31b**−**35b**, **37b**, **39b**, and **43b**−**45b**.* The enone (0.50 mmol, 1 equiv) was added to a mixture of sodium sulfate (220 mg, 1.55 mmol, 3.10 equiv) and *tert*-butyl carbazate (70.8 mg, 0.53 mmol, 1.05 equiv) in 1,2-dichloroethane (0.4 mL) in a pressure tube. The resulting suspension was heated to 85 °C. After 4.5 h, the reaction mixture was allowed to cool to 23 °C. Dichloromethane (1.5 mL) was added, the solution was cooled to 0 °C, and Palau'chlor (221 mg, 1.00 mmol, 2.00 equiv) was added in one portion. After full consumption of the conjugated hydrazone (monitored by TLC), triethylamine (229 μL, 1.65 mmol, 3.10 equiv) was added in one portion, and the suspension was allowed to warm to 23 °C. After 2.5 h, acetone−water (v/v = 9:2, 1.75 mL) and Amberlyst 15 (700 mg) were added, and the suspension was heated to 50 °C. After 14 h at 50 °C, the reaction mixture was allowed to cool to 23 °C and then was diluted with dichloromethane (2 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual solid was suspended in diethyl ether, the suspension was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane or diethyl ether/pentane) to afford the product.

*3-Chlorocyclohex-2-en-1-one (**20b**).* The general procedure was followed, using cyclohex-2-en-1-one (48.1 mg, 0.50 mmol), affording **20b** after purification by flash column chromatography on silica gel (17% diethyl ether in pentane) as a yellow oil (18 mg, 27%). The obtained characterization data were in full agreement with those values reported in the literature.[11a]

*3-Chloro-4,4-dimethylcyclohex-2-en-1-one (**31b**).* The general procedure was followed, using 4,4-dimethylcyclohex-2−1-one (62.1 mg, 0.50 mmol), affording **31b** after purification by flash column chromatography on silica gel (17% diethyl ether in pentane) as a yellow oil (20 mg, 26%). TLC (33% ethyl acetate in hexanes): R_f = 0.75 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H), 2.47 (t, J = 6.8 Hz, 2H), 1.98 (t, J = 7.0 Hz, 2H), 1.3 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 167.8, 127.7, 38.6, 36.7, 34.2, 26.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (w), 2933 (w), 2866 (w), 1687 (vs), 1675 (s), 1596 (m), 1460 (w), 1304 (m), 1270 (w), 991 (w), 967 (m) cm^{-1}. HR-MS (EI): calcd for $(C_8H_{11}O^{35}Cl)^+$ 158.0498, found 158.0477.

*3-Chloro-4-methyl-4-phenylcyclohex-2-en-1-one (**32b**).* The general procedure was followed, using 4-methyl-4-phenylcyclohex-2-en-1-one (93.1 mg, 0.50 mmol), affording **32b** after purification by flash column chromatography on silica gel (9% ethyl acetate in hexane) as a white solid (25 mg, 22%). TLC (33% ethyl acetate in hexanes): R_f = 0.73 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.52−7.25 (m, 5H), 6.41 (s, 1H), 2.44−2.11 (m, 4H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 196.7, 164.6, 143.2, 130.8, 129.2, 127.7, 126.9, 47.6, 39.9, 34.6, 26.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3060 (w), 2973 (w), 1734 (w), 1682 (vs), 1596 (m), 1496 (m), 1445 (m), 1298 (m), 1207 (m), 1071 (w), 970 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{13}O^{35}Cl)^+$ 220.0655, found 220.0651.

*3-Chloro-4,4-diphenylcyclohex-2-en-1-one (**33b**).* The general procedure was followed, using 4,4-diphenylcyclohex-2-en-1-one (124 mg, 0.50 mmol), affording **33b** after purification by flash column chromatography on silica gel (11% ethyl acetate in hexane) as a white solid (25 mg, 18%). TLC (33% ethyl acetate in hexanes): R_f = 0.83 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.42−7.28 (m, 10H), 6.51 (s, 1H), 2.86 (t, J = 6.3 Hz, 2H), 2.23 (t, J = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 196.4, 163.4, 142.5, 131.7, 129.5, 128.8, 128.0, 57.6, 39.3, 35.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3059 (w), 2958 (w), 1681 (s), 1594 (m), 1496 (m), 1448 (m), 1290 (m), 1210 (w), 1171 (w), 980 (m), 949 (w) cm^{-1}. HR-MS (EI): calcd for $(C_{18}H_{15}O^{35}Cl)^+$ 282.0811, found 282.0819.

*Methyl 2-Chloro-1-methyl-4-oxo-2-cyclohexene-1-carboxylate (**34b**).* The general procedure was followed, using methyl 1-methyl-4-oxo-2-cyclohexene-1-carboxylate (134 mg, 0.50 mmol), affording **34b** after purification by flash column chromatography on silica gel (9% ethyl acetate in hexane) as a colorless oil (35 mg, 34%). TLC (33% ethyl acetate in hexanes): R_f = 0.68 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (s, 1H), 3.78 (s, 3H), 2.58−2.40 (m, 3H), 2.12−1.99 (m, 1H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 172.7, 159.3, 129.8, 53.2, 50.2, 34.2, 34.1, 22.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (w), 1735 (s), 1684 (s), 1604 (m), 1454 (m), 1302 (m), 1255 (m) 1196 (m), 1177 (m), 1117 (m), 977 (m) cm^{-1}. HR-MS (EI): calcd for $(C_9H_{11}O_3{}^{35}Cl)^+$ 202.0397, found 202.0388.

*(2-Chloro-1-methyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (**35b**).* The general procedure was followed, using (1-methyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (**66**; 112 mg, 0.50 mmol), affording **35b** after purification by flash column chromatography on silica gel (9% ethyl acetate in hexane) as a yellow oil (32 mg, 24%). TLC (33% ethyl acetate in hexanes): R_f = 0.69 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 4.32 (d, J = 11.1 Hz, 1H), 3.93 (d, J = 11.2 Hz, 1H), 2.56−2.49 (m, 2H), 2.26 (ddd, J = 13.7, 9.5, 6.2 Hz, 1H), 1.91 (ddd, J = 13.7, 6.7, 5.9 Hz, 1H), 1.30 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 178.1, 162.9, 130.0, 68.8, 42.2, 39.0, 33.8, 32.0, 27.2, 21.2. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (w), 2936 (w), 1730 (s), 1678 (s), 1601 (m), 1480 (m), 1461 (m), 1280 (s), 1141 (s) cm^{-1}. HR-MS (EI): calcd for $(C_{13}H_{20}O_3{}^{35}Cl)^+$ (M + H)$^+$ 259.1101, found 259.1110.

*4-((Benzyloxy)methyl)-3-chlorocyclohex-2-en-1-one (**37b**).* The general procedure was followed, using 4-[(phenylmethoxy)methyl]-2-cyclohex-2-en-1-one (108 mg, 0.50 mmol), affording **37b** after purification by flash column chromatography on silica gel (9% ethyl acetate in hexane) as a yellow oil (25 mg, 20%). TLC (33% ethyl acetate in hexanes): R_f = 0.67 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 5H), 6.27 (s, 1H), 4.61−4.51 (m, 2H), 3.75 (d, J = 5.1 Hz, 2H), 2.89−2.82 (m, 1H), 2.56 (ddd, J = 16.6, 9.8, 5.8 Hz, 1H), 2.36 (app dt, J = 17.0, 5.8 Hz, 1H), 2.29−2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 158.7, 137.7, 130.0, 128.5, 127.9, 127.6, 73.4, 69.6, 42.9, 34.2, 25.2. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3031 (w), 2924 (w), 2864 (w), 1725 (w), 1678 (vs), 1604 (m), 1453 (m), 1294 (m), 1282 (m), 1235 (m), 1200 (m), 1100 (s), 979 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{14}H_{15}O_2{}^{36}Cl)^+$ 250.0761, found 250.0763.

*3-Chloro-4-(prop-2-yn-1-yl)cyclohex-2-en-1-one (**39b**).* The general procedure was followed, using 4-(prop-2-yn-1-yl)cyclohex-2-en-1-one (67.1 mg, 0.50 mmol), affording **39b** after purification by flash column chromatography on silica gel (33% ethyl acetate in hexane) as a colorless oil (26 mg, 30%). TLC (33% ethyl acetate in hexanes): R_f = 0.78 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 2.86−2.78 (m, 1H), 2.72 (dt, J = 16.9, 3.2 Hz, 1H), 2.63−2.52 (m, 2H), 2.39 (ddd, J = 17.1, 8.2, 5.0 Hz, 1H), 2.26 (dddd, J = 19.3, 16.1, 11.4, 6.5 Hz, 2H), 2.07 (t, J = 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 159.7, 129.6, 80.5, 71.4, 41.1 34.3, 26.5, 21.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3297 (w), 2931 (w), 1678 (s), 1603 (s), 1432 (w), 1328 (m), 1289 (m), 1237 (m), 1199 (m), 1151 (m), 1091 (w), 972 (s) cm^{-1}. HR-MS (EI): calcd for $(C_9H_8O^{35}Cl)^+$ (M − H)$^+$ 167.0264, found 167.0262.

*3-Chloro-5-phenylcyclohex-2-en-1-one (**43b**).* The general procedure was followed, using 5-phenylcyclohex-2-en-1-one (**61**; 86.1 mg, 0.50 mmol), affording **43b** after purification by flash column chromatography on silica gel (9% ethyl acetate in hexane) as a yellow oil (37 mg, 36%). TLC (33% ethyl acetate in hexanes): R_f = 0.80 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.41−7.32 (m, 2H), 7.32−7.22 (m, 3H), 6.29 (d, J = 1.9 Hz, 1H), 3.61−3.34 (m, 1H), 3.00−2.85 (m, 2H), 2.68−2.60 (m, 2H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 196.3, 157.9, 142.5, 129.37, 128.7, 127.8, 127.2, 43.9, 42.0, 40.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3063 (w), 3030 (w), 1745 (w), 1682

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

(s), 1612 (s), 1496 (w), 1454 (w), 1425 (w), 1370 (w), 1336 (w), 1282 (m), 1254 (m) 1234 (m), 1138 (m), 1038 (w), 1002 (w) cm^{-1}. HR-MS (EI): calcd for $(C_{12}H_{11}O^{35}Cl)^+$ 206.0498, found 206.0499.

*3-Chloro-6-methylcyclohex-2-en-1-one (**44b**).* The general procedure was followed, using 6-methylcyclohex-2-en-1-one (55.8 mg, 0.50 mmol), affording **44b** after purification by flash column chromatography on silica gel (9% diethyl ether in pentane as a colorless oil (16 mg, 22%). TLC (17% diethyl ether in pentanes): R_f = 0.68 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (d, J = 1.9 Hz, 1H), 2.83−2.71 (m, 1H), 2.66 (app dt, J = 18.8, 4.6 Hz, 1H), 2.42−2.30 (m, 1H), 2.13 (ddd, J = 13.7, 10.0, 5.5 Hz, 1H), 1.88−1.75 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 157.5, 127.9, 40.2, 33.6, 30.3, 14.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (m), 2856 (w), 1679 (s), 1616 (m), 1457 (w), 1345 (w), 1193 (w), 1100 (w) cm^{-1}. HR-MS (EI): calcd for $(C_7H_9O^{35}Cl)^+$ 144.0342, found 144.0330.

Preparation of 5-Substituted 1,3,4-Oxadiazolin-2-ones. *General Experimental Procedures for Compounds **50**−**52**.* The α,β-unsaturated aldehyde (0.50 mmol, 1 equiv) was added to a mixture of sodium sulfate (220 mg, 1.55 mmol, 3.10 equiv), and *tert*-butyl carbazate (71 mg, 0.53 mmol, 1.05 equiv) in 1,2-dichloroethane (0.8 mL) in a pressure flask. The resulting suspension was heated to 85 °C. After 4.5 h, the suspension was allowed to cool to 25 °C. Dichloromethane (3 mL) was added, the solution was cooled to 0 °C, and Palau'chlor (210 mg, 1.00 mmol, 2.00 equiv) was added. After full consumption of the hydrazone (monitored by TLC), triethylamine (215 μL, 1.55 mmol, 3.10 equiv) was added in one portion. The resulting thick suspension was stirred for 2 h at 25 °C. Acetone−water (v/v = 9:2, 1.75 mL) and Amberlyst 15 (700 mg) were added, and the suspension was heated to 50 °C. After 14 h, the reaction mixture was allowed to cool to 25 °C and then was diluted with dichloromethane (2 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual oil was purified by flash column chromatography on silica gel (ethyl acetate/hexane) to afford the product.

*5-(2-Phenylethenyl)-1,3,4-oxadiazol-2(3H)-one (**50**).* The general procedure was followed, using *trans*-cinnamaldehyde (63.0 μL, 0.50 mmol), affording **50** after purification by flash column chromatography on silica gel (20% ethyl acetate in hexanes) as a yellow solid (79 mg, 84%). TLC (25% ethyl acetate in hexanes): R_f = 0.31 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.66 (br s, 1H), 7.87 (d, J = 7.0 Hz, 2H), 7.64−7.52 (m, 3H), 7.48 (d, J = 16.4 Hz, 1H), 7.11 (d, J = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 154.2, 154.0, 136.8, 134.6, 129.6, 128.8, 127.6, 110.8. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3309 (br), 3060 (w), 3028 (w), 1868 (w), 1745 (s), 1716 (s), 1643 (m), 1582 (m), 1449 (m), 1339 (s), 1205 (m), 1064 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{10}H_8O_2N_2)^+$ 188.0586, found 188.0579.

*5-(1-Phenylprop-1-en-2-yl)-1,3,4-oxadiazol-2(3H)-one (**51**).* The general procedure was followed, using α-methyl-*trans*-cinnamaldehyde (71.0 μL, 0.50 mmol), affording **51** after purification by flash column chromatography on silica gel (5% to 33% ethyl acetate in hexanes) as a colorless crystalline solid (32 mg, 31%). TLC (25% ethyl acetate in hexanes): R_f = 0.23 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.41 (s, 1H), 7.51−7.29 (m, 6H), 2.21 (d, J = 1.4 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 157.2, 154.6, 135.4, 133.8, 129.5, 128.4, 128.3, 120.9, 12.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3235 (br), 1770 (s), 1630 (w), 1576 (w), 1448 (w), 1370 (w), 1101 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{11}H_9O_2N_2)^+$ $(M - H)^+$ 201.0664, found 201.0657.

*5-(1-Propen-1-yl)-1,3,4-oxadiazol-2(3H)-one (**52**).* The general procedure was followed, using crotonaldehyde (41 μL, 0.50 mmol), affording **52** after purification by flash column chromatography on silica gel (20% ethyl acetate in hexanes) as a yellowish crystalline solid (7 mg, 11%). TLC (33% ethyl acetate in hexanes): R_f = 0.35 (UV, $KMnO_4$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.18 (br s, 1H), 6.76−6.48 (m, 1H), 6.18−5.94 (m, 1H), 1.94 (dd, J = 6.9, 1.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 154.7, 138.4, 114.5, 18.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3226 (br), 3142 (br), 1765 (s), 1668 (w), 1578 (w), 1441 (w), 1351 (m) cm^{-1}. HR-MS (EI): calcd for $(C_5H_6O_2N_2)^+$ 126.0429, found 126.0427.

Synthesis of the Tetrahydrocarbazolone Fragment of Jerantinine E. *Enaminone **55**.* To an oven-dried pressure tube were added chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (367 mg, 0.51 mmol, 0.10 equiv), SPhos (209 mg, 0.51 mmol, 0.10 equiv), sodium *tert*-butoxide (733 mg, 7.63 mmol, 1.50 equiv), 3,4-dimethoxyaniline (**54**; 1.17 g, 7.63 mmol, 1.50 equiv), and toluene (25 mL). 4-((Benzyloxy)methyl)-3-bromocyclohex-2-enone (**37a**; 1.50 g, 5.09 mmol, 1 equiv) was added, and the dark red suspension was heated to 60 °C for 18 h. The reaction mixture was allowed to cool to 23 °C and was filtered through a short plug of Celite. The filter cake was washed with dichloromethane (50 mL). The filtrate was concentrated, and the residual brown oil was purified by flash column chromatography on silica gel (1% to 2% methanol in dichloromethane) to afford **55** as a brown solid (1.02 g, 55%). TLC (3% methanol in dichloromethane): R_f = 0.12 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.62 (s, 1H), 7.40−7.28 (m, 5H), 6.82 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 8.5, 2.4 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 5.30 (s, 1H), 4.67−4.55 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.73−3.63 (m, 2H), 2.89 (tt, J = 9.1, 4.6 Hz, 1H), 2.28 (td, J = 6.0, 5.4, 2.1 Hz, 2H), 2.07−1.94 (m, 2H), 1.88−1.76 (m, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 196.7, 165.1, 150.0, 147.7, 138.0, 131.9, 129.1, 128.5, 128.4, 117.2, 112.2, 109.3, 98.7, 74.0, 73.8, 56.5, 56.3, 38.7, 35.1, 25.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3249 (br), 2933 (w), 2360 (w), 2340 (w), 1578 (s), 1509 (s), 1462 (m), 1412 (w), 1235 (m), 1201 (m), 1158 (w), 1099 (w), 1026 (m) cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{25}O_4N)^+$ 367.1784, found 367.1771.

*Tetrahydrocarbazolone **56**.* A solution of enaminone **55** (201 mg, 0.56 mmol, 1 equiv) in *N*,*N*-dimethylformamide (6.8 mL) was added to an oven-dried pressure tube containing palladium(II) acetate (12.3 mg, 0.05 mmol, 0.10 equiv), copper(II) acetate (298 mg, 1.64 mmol, 3.00 equiv), and potassium carbonate (227 mg, 1.64 mmol, 3.00 equiv). The resulting green-brown mixture was stirred at 140 °C. After 19 h, the reaction mixture was allowed to cool to 23 °C, and the dark solution was filtered through a short plug of Celite. The filter cake was washed with dichloromethane (60 mL). The filtrate was washed with 10% aqueous ammonia solution (100 mL), and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual black oil was purified by flash column chromatography on triethylamine pretreated silica gel (2% methanol in dichloromethane) to afford **56** as a brown solid (152 mg, 76%). TLC (2% methanol in dichloromethane): R_f = 0.31 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.51 (br s, 1H), 7.62 (s, 1H), 7.47−7.32 (m, 5H), 6.87 (s, 1H), 4.73−4.62 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.78 (dd, J = 9.1, 4.7 Hz, 1H), 3.69 (app t, J = 9.6 Hz, 1H), 3.43 (tt, J = 10.1, 4.8 Hz, 1H), 2.58−2.49 (m, 2H), 2.18−2.08 (m, 1H), 1.92−1.76 (m, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 193.9, 151.8, 148.0, 147.3, 138.3, 130.3, 129.1, 128.5, 128.4, 117.7, 112.9, 103.4, 95.5, 74.0, 74.0, 56.6, 56.5, 37.7, 35.1, 26.8. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3223 (br), 2939 (w), 1624 (s), 1464 (s), 1446 (w), 1321 (w), 1300 (m),1136 (m). HR-MS (ESI): calcd for $(C_{22}H_{24}O_4N)^+$ $(M + H)^+$ 366.1705, found 366.1696.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic data for allylic bromide **22**, and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the FCI (Liebig Fellowship to T.M.), the Dr. Klaus Römer-Foundation (Römer Fellowship to T.H.), and the DFG (Emmy-Noether Fellowship to T.M.). We thank Dr. Peter Mayer (LMU Munich) for X-ray structure analysis and Dr. Kevin Mellem for helpful discussions during the preparation of this manuscript.

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DOI: 10.1021/jo502809d
J. Org. Chem. 2015, 80, 2281−2294