

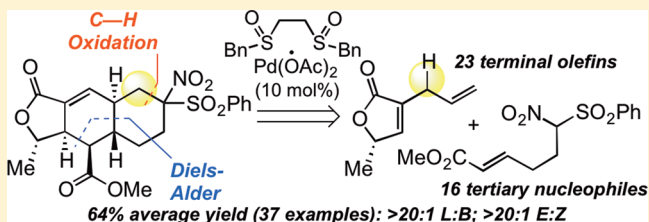
# General Allylic C–H Alkylation with Tertiary Nucleophiles

Jennifer M. Howell, Wei Liu, Andrew J. Young,<sup>†</sup> and M. Christina White\*

Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana–Champaign, Urbana, Illinois, 61801, United States

## Supporting Information

**ABSTRACT:** A general method for intermolecular allylic C–H alkylation of terminal olefins with tertiary nucleophiles has been accomplished employing palladium(II)/bis(sulfoxide) catalysis. Allylic C–H alkylation furnishes products in good yields (avg. 64%) with excellent regio- and stereoselectivity (>20:1 linear:branched, >20:1 *E*:*Z*). For the first time, the olefin scope encompasses unactivated aliphatic olefins as well as activated aromatic/heteroaromatic olefins and 1,4-dienes. The ease of appending allyl moieties onto complex scaffolds is leveraged to enable this mild and selective allylic C–H alkylation to rapidly diversify phenolic natural products. The tertiary nucleophile scope is broad and includes latent functionality for further elaboration (e.g., aliphatic alcohols,  $\alpha,\beta$ -unsaturated esters). The opportunities to effect synthetic streamlining with such general C–H reactivity are illustrated in an allylic C–H alkylation/Diels–Alder reaction cascade: a reactive diene is generated *via* intermolecular allylic C–H alkylation and approximated to a dienophile contained within the tertiary nucleophile to furnish a common tricyclic core found in the class I galbulimima alkaloids.



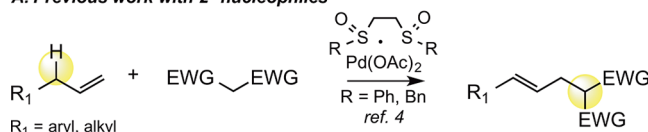
## INTRODUCTION

The development of general C–H to C–C bond transformations that enable novel disconnections in the retrosynthesis of carbon skeletons stands to profoundly impact organic synthesis.<sup>1</sup> While substantial progress has been achieved in the alkylation of  $sp^2$  C–H bonds, methods for  $sp^3$  C–H bond alkylation are scarce.<sup>2</sup>

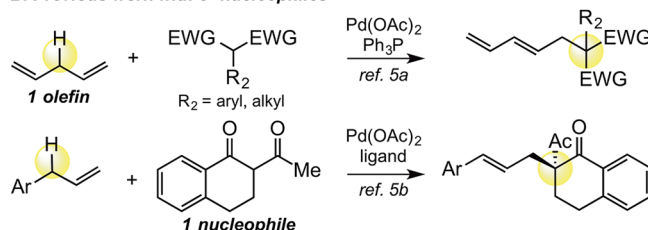
We and others have shown palladium(II)/bis(sulfoxide) catalysis to be a powerful platform for allylic C–H oxidations, aminations, dehydrogenations, halogenations and alkylations of  $\alpha$ -olefin substrates.<sup>3,4</sup> Unfortunately, C–H alkylation methods have been limited in scope to disubstituted methylene nucleophiles bearing two electron-withdrawing groups (Scheme 1A). Previous reports employing tertiary nucleophiles in allylic C–H alkylation reactions have been limited with respect to either olefin scope (i.e., only 1,4-dienes) or nucleophile scope (i.e., tetralones) (Scheme 1B).<sup>5,6</sup> We recognized that a general method for intermolecular allylic C–H alkylation using tertiary nucleophiles<sup>6</sup> with high levels of flexibility in the  $R_4$  group would be very powerful (Scheme 1C). Incorporation of functionality in the nucleophile that can be further elaborated, for example in the context of complexity generating reactions, would enable the rapid construction of topologically varied carbon frameworks from simple building blocks. Herein, we disclose the first general allylic C–H alkylation reaction with tertiary nucleophiles. In contrast to previous allylic C–H alkylations, the method described herein enables coupling of two complex and valuable fragments to directly afford a target molecule. For example, Pd(II)/bis(sulfoxide)-catalyzed allylic C–H alkylation is used to generate reactive intermediates which concomitantly engage in intramolecular Diels–Alder cycloadditions *in situ*, leading to the

## Scheme 1. Allylic C–H Alkylation of 3° Nucleophiles

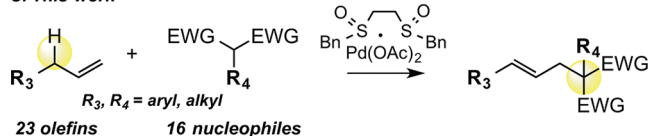
### A. Previous work with 2° nucleophiles



### B. Previous work with 3° nucleophiles



### C. This work



rapid assembly of highly functionalized decalin core structures found in the galbulimima alkaloids.

## RESULTS AND DISCUSSION

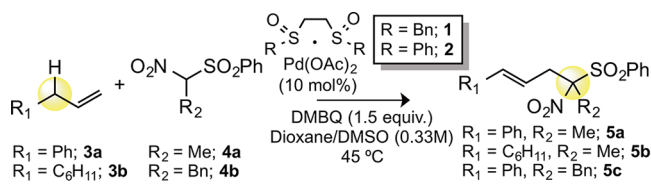
**Reaction Development.** Our investigation began with a prototypical nucleophile, ((1-nitroethyl)sulfonyl)benzene (**4a**).

Received: January 24, 2014

Published: March 18, 2014

We were delighted to find that upon reaction with allylbenzene (**3a**) under our reported conditions<sup>4c</sup> this tertiary nucleophile

Table 1. Reaction Development



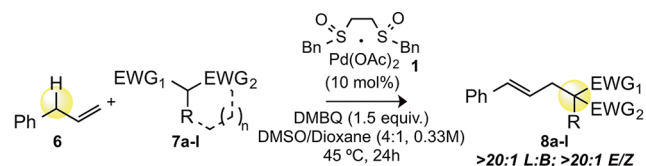
Entry <sup>a</sup>	Olefin	Tertiary Nucleophile	Catalyst	Dioxane/DMSO	Yield (%) <sup>b</sup>	L:B <sup>c</sup>	E:Z <sup>c</sup>
1	<b>3a</b>	<b>4a</b>	<b>1</b>	4:1	61	> 20 : 1	> 20 : 1
2 <sup>d</sup>	<b>3b</b>	<b>4a</b>	<b>1</b>	4:1	35	> 20 : 1	> 20 : 1
3	<b>3a</b>	<b>4a</b>	<b>1</b>	1:4	83	> 20 : 1	> 20 : 1
4 <sup>e</sup>	<b>3b</b>	<b>4a</b>	<b>1</b>	1:4	58	> 20 : 1	> 20 : 1
5	<b>3a</b>	<b>4a</b>	<b>2</b>	1:4	74	> 20 : 1	> 20 : 1
6 <sup>f</sup>	<b>3b</b>	<b>4a</b>	<b>2</b>	1:4	41	> 20 : 1	> 20 : 1
7	<b>3a</b>	<b>4a</b>	Pd(OAc) <sub>2</sub>	1:4	11	—	—
8	<b>3a</b>	<b>4b</b>	<b>1</b>	1:4	78	> 20 : 1	> 20 : 1

<sup>a</sup>Reaction conditions: **3** (1 equiv), **4** (2 equiv), **1** or **2** (10 mol %), 2,6-dimethylbenzoquinone (DMBQ) (1.5 equiv), 0.33 M dioxane/DMSO, 45 °C, 24 h. <sup>b</sup>Isolated yield, average of two runs. <sup>c</sup>Ratio determined by <sup>1</sup>H NMR analysis of crude reaction mixture. <sup>d</sup>72 h, 29% yield after 24 h. <sup>e</sup>72 h; 52% yield after 24 h. <sup>f</sup>72 h.

engaged in alkylation to afford the desired alkylated product **5a** in 61% yield (Table 1, entry 1). Evaluation of a nonactivated, aliphatic terminal olefin substrate, allylcyclohexane (**3b**), afforded the desired product **5b**, albeit in a modest yield (35% yield, entry 2). Encouragingly, both reactions proceeded with excellent regio- and stereoselectivity (>20:1 linear:branched, >20:1 E:Z). We reasoned that functionalization of a  $\pi$ -allylPd intermediate with a sterically bulky tertiary nucleophile was sluggish and may be accelerated by increasing the amount of DMSO, previously shown to be a ligand that promotes functionalization.<sup>4c</sup> Consistent with this hypothesis, shifting the solvent/DMSO ratio from 4:1 to 1:4 improved the yield with an activated allylbenzene substrate to 83% (entry 3), and that of the unactivated allylcyclohexane substrate to 58% (entry 4). Evaluation of the commercially available phenylbis(sulfoxide) catalyst **2** resulted in diminished yield (entry 5 and entry 6); high concentrations of DMSO are thought to interfere with reassociation of the aryl bis(sulfoxide) ligand to form complex **2**, which is required for C–H cleavage.<sup>4c</sup> The yield was dramatically decreased to 11% when Pd(OAc)<sub>2</sub> was utilized (entry 7), illustrating the important role of the aryl bis(sulfoxide) ligand for C–H alkylation under mild conditions. A preliminary evaluation of varying the R<sub>2</sub> group from methyl (**4a**) to benzyl (**4b**) suggested that this reaction would be general (78% yield, entry 8).

**Tertiary Nucleophile Scope.** Incorporation of various functional groups into the nucleophile would greatly extend the synthetic utility of the Pd(II)/bis(sulfoxide)-catalyzed allylic C–H alkylation reaction. Latent functionality could be brought in as part of the nucleophile and unmasked at a later stage to facilitate further elaboration. A variety of functionalities, including sulfonyl, nitro, ketone, and ester moieties were found to be suitable electron-withdrawing groups (Table 2). 2-Nitropropiophenones as well as a tetralone derivative all proved to be competent nucleophiles (**8a–d**). Substitution of the

Table 2. Tertiary Nucleophiles for C–H Alkylation



**$\alpha$ -Nitro Carbonyls**

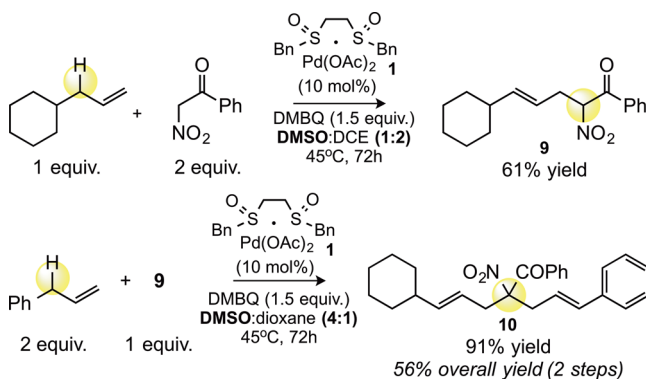
X = H; **8a** 57%  
 = Cl; **8b** 59%  
 = OMe; **8c** 50%<sup>b</sup>

**8d** 76%  
**8e** 58%  
**8f** 80%<sup>c</sup>  
**8g** 53%  
**8h** 61%  
**8i** 72%  
**8j** 62%  
**8k** 66%  
**8l** 68%

**Carbonyls**

<sup>a</sup>Reaction conditions: allylbenzene **6** (1 equiv), **7** (2 equiv), **1** (10 mol %), 2,6-dimethylbenzoquinone (DMBQ) (1.5 equiv), DMSO/dioxane (4:1, 0.33 M), 45 °C, 24 h. Products isolated as one regio- and stereoisomer. Isolated yield is the average yield of two runs. <sup>b</sup>**7c** (3 equiv). <sup>c</sup>**6** (2 equiv), **7f** (1 equiv); 52% yield using **6** (1 equiv), **7f** (2 equiv).

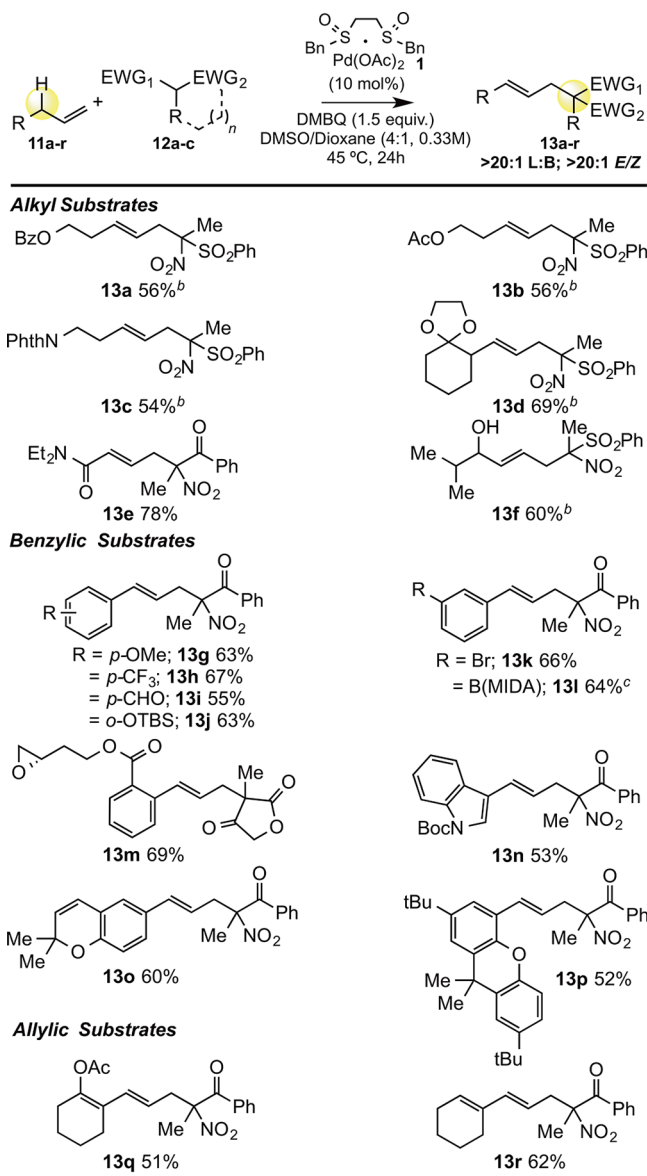
Scheme 2. Sequential Allylic C–H Alkylation Strategy



benzoyl aromatic ring was tolerated, including an aryl chloride, which provides a handle for further derivatization (**8b**, **8c**). The R alkyl substituent of the nucleophile was varied to longer chains, including ones incorporating oxygen functionality suitable for additional elaboration (**8e**, **8f**). Notably, for reactions in which the nucleophile-coupling partner is particularly valuable, it may be used in limiting quantities with good yields (**8f**). Nucleophile pK<sub>a</sub> dependence on reactivity was noted, consistent with the notion that the nucleophile must undergo facile keto–enol tautomerization or deprotonation by endogenous base *in situ*. We were encouraged to find that an  $\alpha$ -nitropropiophenone and  $\beta$ -ketoester, less acidic pro-nucleophiles, engaged in alkylation (**8g**, **8h**).

Methyl tetronic acid and methyl Meldrum's acid, two highly acidic dicarbonyl compounds, were found to be suitable nucleophiles (**8i**, **8j**). Tricarbonyls also proved to be competent tertiary nucleophiles (**8k**, **8l**). It is significant to note that these nucleophiles allow for the construction of quaternary centers via the allylic C–H alkylation reaction.<sup>7</sup>

Table 3. Terminal Olefins for C–H Alkylation

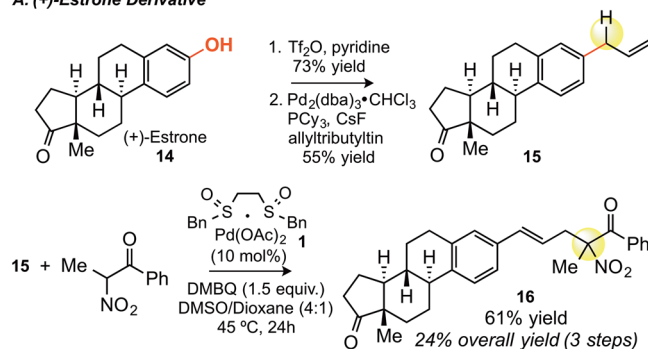


<sup>a</sup>Reaction conditions:  $\alpha$ -olefin **11** (1 equiv), **12** (2 equiv), **1** (10 mol %), 2,6-dimethylbenzoquinone (DMBQ) (1.5 equiv), DMSO/dioxane (4:1, 0.33 M), 45 °C, 24 h. Products isolated as one regio- and stereo-olefin isomer. Isolated yield, average yield of two runs. <sup>b</sup>72 h. <sup>c</sup>MIDA = methyliminodiacetate.

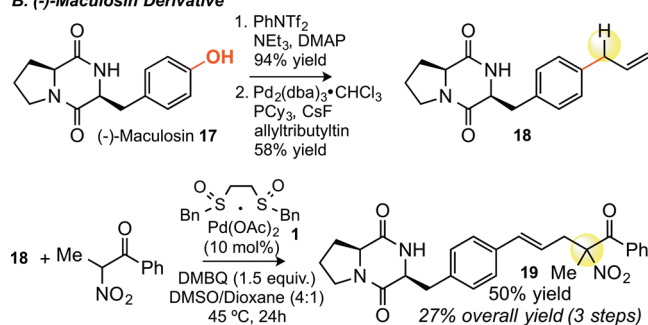
A general strategy to build tertiary nucleophiles containing internal olefins is afforded by exploiting the divergent reactivity of our previously reported conditions<sup>4c</sup> and those of the present work. Allylic alkylation of a terminal aliphatic olefin (i.e., allylcyclohexane) with a secondary nucleophile (i.e., benzoyliminotromethane) under conditions using minimal amounts of DMSO furnished monoalkylated product **9** (Scheme 2). Under conditions employing higher concentrations of DMSO, **9** may

Scheme 3. Diversification of Natural Products

A. (+)-Estrone Derivative



B. (-)-Maculosin Derivative

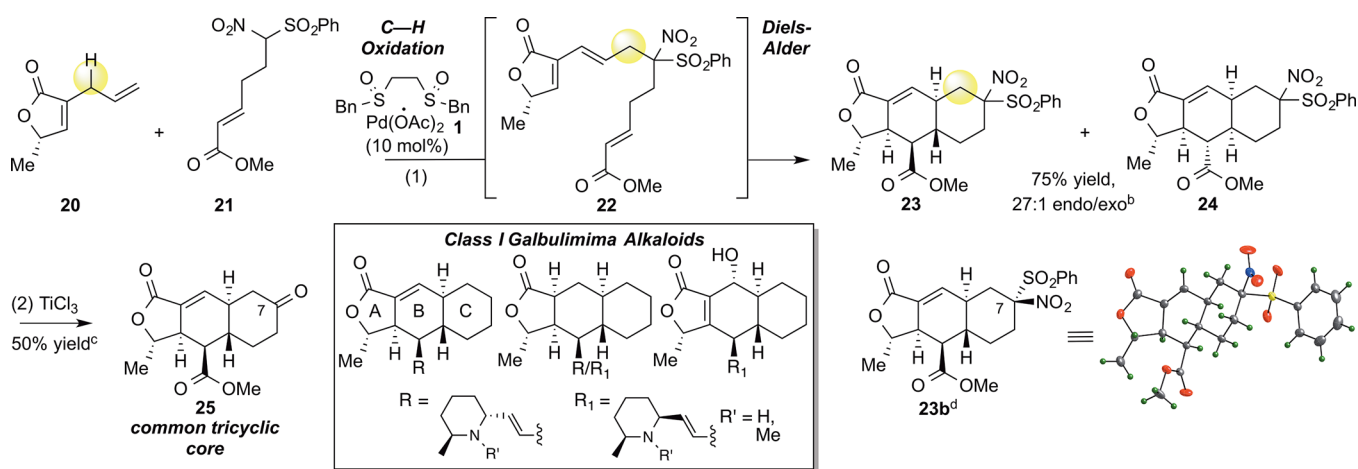


be used as a tertiary nucleophile to produce the fully substituted compound **10** in 91% yield. The two-step reaction sequence proceeded in 56% overall yield and incorporated all but four hydrogen atoms of the substrates in the final product. Notably, all Pd/bis(sulfoxide)-catalyzed allylic C–H functionalizations, including C–H alkylation, are highly chemoselective for terminal olefins with internal olefins being well-tolerated.<sup>3,4</sup>

**Terminal Olefin Scope.** Upon investigation of the  $\alpha$ -olefin substrate scope, we were delighted to find that, in contrast to previously reported methods, our reaction was capable of alkylating unactivated aliphatic  $\alpha$ -olefins with tertiary nucleophiles in good yields and excellent selectivities (Table 3). Primary alcohol and amine functionalities masked as benzoate/acetate esters and phthalimides were well tolerated (**13a**, **13b**, **13c**). Terminal olefin substrates bearing acetals and amides also proved to be competent alkylation partners (**13d**, **13e**). Most notably, an unprotected secondary alcohol substrate participated in the alkylation reaction in good yield (**13f**). This example underscores the remarkable chemoselectivity of this allylic C–H functionalization method and its orthogonality to standard base-promoted alkylation methods (alcohol  $pK_a \approx 15$ ; allylic C–H bond  $pK_a \approx 42$ ).

Additionally, we found that a variety of allylarene and heteroarenes were readily alkylated. *Para*, *meta*, and *ortho* substitution of electronically varied groups were all well tolerated on allylbenzene substrates (**13g**, **13h**, **13i**, **13j**). Significantly, bromine and boron substituents, which may be further elaborated via traditional Pd(0) cross-coupling methods, could also be present in the substrate (**13k**, **13l**). Highly reactive electrophiles, such as aldehydes and terminal epoxides, may also be incorporated into the olefin substrate, highlighting the high chemoselectivity of this reaction for functionalization of the electrophilic  $\pi$ -allylpd intermediate (**13i**, **13m**). Allylic C–H alkylation is also tolerant of a range of medically important heterocyclic aromatic functionalities such as indole and chromene (**13n**, **13o**), as well as xanthene, important in



Scheme 4. Tandem Allylic C–H Alkylation/Diels–Alder Reaction Cascade<sup>a,b,c,d</sup>

<sup>a</sup>Reaction conditions: (1)  $\alpha$ -olefin **20** (1 equiv), **21** (1.8 equiv), **1** (10 mol %), 2,6-dimethylbenzoquinone (DMBQ) (1.5 equiv), DMSO/dioxane (4:1, 0.33 M), 45 °C, 24 h followed by warming to 55 °C, 48 h, (2) 20% TiCl<sub>3</sub> in 3% HCl, THF, rt. <sup>b</sup>Endo/exo isomers **23** and **24** result from addition anti to the methyl group of the butenolide. The endo isomer resulting from syn addition was also observed (6:1 endo-anti/endo-syn). <sup>c</sup>50% yield after one recycle. Isolated as a 5:1 mixture of diastereomers, major diastereomer shown. <sup>d</sup>**23b** was confirmed by X-ray crystallographic analysis.

synthetic and material science applications (**13p**). Notably, in all cases with allyl aromatics, high regioselectivity was observed for formation of linear alkylation products. The observed regioselectivity we believe is steric in nature, arising from nucleophilic attack at the least hindered terminus of the  $\pi$ -allylPd intermediate. This contrasts with our previous observations of variable regioselectivity in the functionalization of allylarenes with disubstituted methylene nucleophiles.<sup>4a,c</sup> Finally, 1,4-diene substrates were also alkylated in good yields and high selectivities to furnish 1,3-diene products that may be further elaborated to generate skeletal complexity (*vide infra*) (**13q**, **13r**).

**Late-Stage Allylic C–H Alkylation of Natural Product Derivatives.** Rapidly accessing molecular diversity at a late stage from bioactive natural product skeletons is a promising strategy for identifying drug candidates.<sup>8</sup> Phenolic natural products are abundant and generally readily available in large quantities from commercial sources. We envisaged that by combining powerful allylation reactions with our mild and selective allylic C–H alkylation we could provide a general strategy to rapidly diversify phenolic natural products. A range of carbon nucleophiles may be used that can also be further elaborated. As proof of principle, the common steroid hormone (+)-estrone (**14**) was derivatized via a short synthetic route (Scheme 3). Triflate formation followed by Stille cross-coupling rapidly appends the allyl moiety, furnishing allylarene **15**. We were delighted that exposure of **15** and 2-nitropropiophenone to the catalytic Pd(II)/bis(sulfoxide) reaction conditions afforded alkylated product **16** in high yield (61% yield, 24% yield over three steps, 63% average yield per step). Markedly, C–H alkylation takes place in the presence of an enolizable ketone, again demonstrating the orthogonal nature of this C–H functionalization reaction to base-mediated alkylation methods. Similarly, (–)-maculosin (**17**), a naturally occurring diketopiperazine phytotoxin, was readily functionalized to provide **19** in good yield (50% yield, 27% yield over three steps, 65% average yield per step). Highlighting the high functional group tolerance of this allylic C–H functionalization method, alkylation proceeded smoothly in the presence of a secondary amide capable of coordinating to and deactivating the palladium catalyst.

### Molecular Complexity via C–H Alkylation: A Tandem Allylic C–H Alkylation/Diels–Alder Reaction Cascade.

Catalytic allylic C–H alkylation holds tremendous potential for directly accessing synthetic intermediates, which may subsequently be coupled to secondary complexity-generating reactions to rapidly forge new carbon frameworks. We recently demonstrated this in the context of a dehydrogenative Diels–Alder reaction wherein the reactive diene was generated via an allylic C–H dehydrogenation reaction.<sup>3f</sup> Given the generality in scope of the allylic alkylation reaction, we questioned if we could effect a tandem allylic C–H alkylation/Diels–Alder reaction cascade wherein a reactive diene intermediate is generated during C–H alkylation and approximated to a dienophile contained within the tertiary nucleophile. We became particularly interested in applying such a strategy to an efficient synthesis of the galbulimima alkaloid core whose structures have attracted much interest from both the synthetic and medicinal communities.<sup>9</sup> Whereas current synthetic routes to these alkaloids have primarily limited chemical derivatizations to the appended heterocyclic R/R<sub>1</sub> group, an allylic C–H alkylation/Diels–Alder route could rapidly access ketone **25**, which offers an additional synthetic handle for derivatization of the C ring of the tricyclic core. Upon exposure of the skipped diene  $\alpha$ -olefin **20** and dienophile-containing tertiary nucleophile **21** to the Pd(II)/bis(sulfoxide)-catalyzed allylic C–H alkylation reaction conditions, we were pleased to observe formation of tricycles **23** and **24** in excellent yield (75% yield, 87% yield per step) and outstanding endo selectivity (27:1 endo/exo) (Scheme 4). Shorter reaction time confirmed that the reaction proceeds via initial allylic C–H alkylation to afford isolated intermediate diene **22** (see Supporting Information [SI]), which subsequently engages in a highly endoselective intramolecular Diels–Alder cycloaddition with the appended  $\alpha,\beta$ -unsaturated ester to furnish the tricycles (**23**, **24**). The tricyclic structure of **23b**, a C7 epimer of the endo series, was confirmed via X-ray crystallographic analysis. Subsequent treatment of the mixture with a Lewis acid solution efficiently converted the  $\alpha$ -nitro sulfone to the corresponding ketone **25** (50% yield), providing primarily the endo diastereomer that appears in the galbulimima alkaloid core.

## ■ CONCLUSION

In summary, we have disclosed a palladium(II)/bis(sulfoxide)-catalyzed allylic C–H alkylation reaction that features unprecedented generality in scope of both the olefin and the tertiary nucleophile. Aliphatic terminal olefins containing reactive functionalities such as unprotected secondary alcohols, amides, ketals, and internal olefins are viable substrates, as are allylarenes containing reactive electrophiles such as aldehydes, and terminal epoxides, as well as heterocyclic moieties such as indoles and diketopiperazines. Cyclic and acyclic tertiary nucleophiles with appended  $\alpha,\beta$ -unsaturated esters, masked aliphatic alcohols, or dense carbonyl functionality readily engage in functionalization. The ability to synthetically tailor both intermolecular reaction partners has enabled C–H alkylation to be used to generate intermediates that can undergo intramolecular secondary reactions to rapidly construct complex molecular architectures from simple linear starting materials.

## ■ EXPERIMENTAL PROCEDURES

**General Procedure for the Allylic C–H Alkylation (Table 2).** An oven-dried, one dram (4 mL, borosilicate) vial fitted with a Teflon magnetic stir bar was charged with Pd[1,2-bis(benzylsulfinyl)ethane]-(OAc)<sub>2</sub> **1** (0.10 equiv, 0.030 mmol) and 2,6-dimethylbenzoquinone (DMBQ) (1.5 equiv, 0.45 mmol). The  $\alpha$ -olefin (1 equiv, 0.30 mmol), nucleophile (2.0 equiv, 0.60 mmol), dimethylsulfoxide (DMSO) (0.72 mL), and 1,4-dioxane (0.18 mL) were added sequentially to the reaction vial. The reaction setup is performed open to the atmosphere. The reaction vial was capped and stirred at 45 °C for 24 h in an oil bath. The reaction vial was cooled to room temperature, and the reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl solution (40 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (SiO<sub>2</sub>, EtOAc/hexanes mixtures) provided the pure linear product.

**Preparation of ((Nitromethyl)sulfonyl)benzene, Synthetic Precursor to ((1-Nitroethyl)sulfonyl)benzene (4a).** The known compound was prepared following the improved procedure of Prakash and co-workers.<sup>10</sup> We observed lower reactivity for both benzyl and alkyl substrates when an older literature procedure was employed.<sup>11</sup> Alternatively, ((nitromethyl)sulfonyl)benzene (NSM) purchased from Sigma-Aldrich and methylated following the standard procedure (see SI) afforded alkylation products in yield comparable to that of the corresponding reactions run with nucleophile synthesized via the procedure of Prakash and co-workers.<sup>10</sup>

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental procedures, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

white@scs.illinois.edu

### Present Address

<sup>†</sup>Dow Chemical, 2301 N. Brazosport Blvd., Freeport, Texas 77541, United States.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support was provided by the NIH/NIGMS (2R01 GM 076153B). We thank Dr. Christopher J. Welch and Dr. Erik L. Regalado at Merck for assistance in purification of cycloadducts

**23 and 24 and 25** via supercritical fluid chromatography (SFC). We thank Dr. Lingyang Zhu for assistance with 2D NMR spectroscopic data, and Dr. Jeffery Bertke and Dr. Danielle Gray for crystallographic data. We thank Mr. Stephen E. Ammann and Dr. Paul Gormisky for checking experimental procedures (Table 3, entries 13a and 13b). We thank Ms. Alexandria Brucks for initial investigations. We thank Johnson Matthey for a gift of Pd(OAc)<sub>2</sub> and Sigma-Aldrich for a gift of catalyst **2**.

## ■ REFERENCES

- (1) (a) Engle, K. M.; Yu, J.-Q.; Davies, H. M. L.; Xi, Z.; You, S.-L.; Shi, Z.-J. In *Organic Chemistry: Breakthroughs and Perspectives*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2012; pp 279–333.
- (b) Rousseaux, S.; Liégault, B.; Fagnou, K. In *Modern Tools for the Synthesis of Complex Bioactive Molecules*; John Wiley & Sons, Inc.: New York, 2012; pp 1–32.
- (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.
- (d) Chen, D. Y. K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452.
- (e) White, M. C. *Synlett* **2012**, 2746.
- (f) White, M. C. *Science* **2012**, *335*, 807.
- (2) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
- (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.
- (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
- (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
- (e) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, *41*, 1512.
- (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
- (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
- (h) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382.
- (i) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253.
- (j) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.
- (3) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
- (b) Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.
- (c) Strambeanu, I. I.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 12032.
- (d) Fraunhofer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.
- (e) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316.
- (f) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892.
- (g) Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.
- (4) (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090.
- (b) Lin, S.; Song, C. X.; Cai, G. X.; Wang, W. H.; Shi, Z. J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.
- (c) Young, A. J.; White, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6824.
- (5) (a) Trost, B. M.; Hansmann, M. M.; Thaisrivongs, D. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4950.
- (b) Trost, B. M.; Thaisrivongs, D. A.; Donckele, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1523.
- (6) A tertiary nucleophile is defined herein as any molecule having a carbon atom with three non-hydrogen substituents.
- (7) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.
- (8) (a) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224.
- (b) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829.
- (c) Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281.
- (d) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.
- (e) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.
- (f) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216.
- (g) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.
- (9) (a) Rinner, U.; Lentsch, C.; Aichinger, C. *Synthesis (Stuttgart)* **2010**, 3763.
- (b) Darroch, S.; Taylor, W.; Choo, L. K.; Mitchelson, F. *Eur. J. Pharmacol.* **1990**, *183*, 1720.
- (c) Darroch, S. A.; Taylor, W. C.; Choo, L. K.; Mitchelson, F. *Eur. J. Pharmacol.* **1990**, *182*, 131.
- (d) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron* **2002**, *58*, 9903.
- (e) Miller, J. H.; Aagaard, P. J.; Gibson, V. A.; McKinney, M. J. *Pharmacol. Exp. Ther.* **1992**, *263*, 663.
- (f) Chackalamannil, S.; Xia, Y. *Expert Opin. Ther. Pat.* **2006**, *16*, 493.
- (10) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Ni, C. F.; Haiges, R.; Olah, G. A. *Org. Lett.* **2012**, *14*, 3260.
- (11) Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S. *J. Org. Chem.* **1981**, *46*, 765.