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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Experimental and Computational Studies on Interrupted Nazarov Reactions: Exploration of Umpolung Reactivity at the α-Carbon of Cyclopentanones

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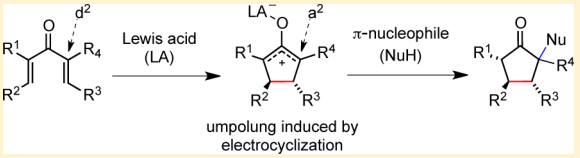
Supporting Information

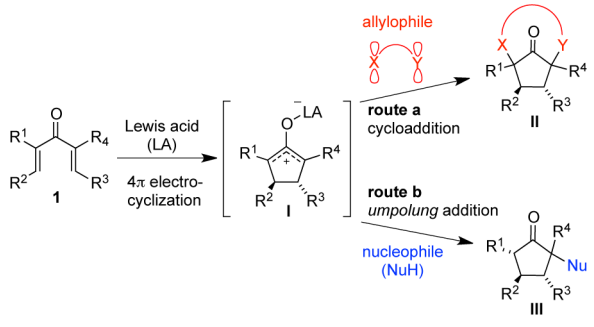
ABSTRACT: A set of densely substituted, α-functionalized cyclopentanones can be generated by a two-component, domino reaction sequence entailing the Nazarov electrocyclization of divinyl ketones and nucleophilic addition of the resulting 2-oxidocyclopentenyl cations by selected trapping modalities. Bypassing the typical eliminative termination, Nazarov oxyallyl species can react with carbon π-nucleophiles through cycloadditions (or formal cycloadditions), in which bridged bicyclic systems are established, or nucleophilic trappings whereby one terminal carbon of the oxyallyl intermediate is subjected to carbon−carbon bond formation. A detailed investigation of reaction parameters to explicitly control the course of the "interrupted" Nazarov reactions is described. This methodology allows for facile installation of α-quaternary centers bearing allyl, alkynyl, and heteroaryl groups in an umpolung fashion. In addition, the trapping event of a Nazarov intermediate with furan was studied by DFT computations, in conjunction with experimental data, offering a rationale for the observed reaction pattern and diastereoselectivity.



INTRODUCTION

Beyond the conventional capacity for accessing cyclopentenones, the Nazarov cyclization[1] can serve as a springboard for cationic domino reaction sequences furnishing a wide range of structure types, collectively termed "interrupted Nazarov reactions".[2] In particular, the mechanistic fate of oxyallyl cations derived from the initial electrocyclization can be diversified in the presence of intermolecular carbon-based traps, bypassing the normal eliminative termination. The Nazarov oxyallyl species, as three-carbon reactive components, can be arrested by allylophiles in cycloaddition reactions, furnishing keto-bridged bicyclic adducts **II** (Scheme 1, route a). For instance, oxyallyl cation **I** has been shown to participate effectively in [4 + 3] cycloadditions with furan and dienes[3] and [3 + 2] formal cycloadditions with allylsilanes[4] and vinyl sulfides.[5]

Scheme 1. Intercepting the Nazarov Intermediate with Intermolecular Trapping Agents



While the scope of this chemistry in constructing bridged polycarbocycles **II** is well established, examples regarding the selective functionalization at one terminus of the cyclized allylic cation **I** most often have involved heteroatom nucleophiles such as halides,[6] nitrogen,[7] and oxygen nucleophiles.[8] Inspired by this concern, we have recently devoted efforts to expand the synthetic capacities of the "interrupted Nazarov" reaction by generalizing the reactivity mode wherein electrocyclization is followed by nucleophilic addition by carbon nucleophiles (Scheme 1, route b).[9] A key feature of this reaction cascade lies in 2-oxyallyl cation **I** acting as an electrocyclization-induced umpolung of the carbonyl α-carbon.[10] Due to the carbon functionality being installed, the products would serve as useful building blocks in the construction of cyclopentanoid derivatives; advantageously, the ketone **III**, which still bears an enolizable carbon, could presumably be converted to more elaborate products through enolate chemistry.

We present herein a comprehensive survey, exploiting the Nazarov reaction as an initiation of umpolung bond-forming processes that allows facile synthesis of diverse α-functionalized cyclopentanone products with well-defined stereochemistry. To gain insight into the mechanism and the origin of stereoselectivity, we also describe *in silico* investigations on the interrupted Nazarov reactions involving furan as the trapping agent.

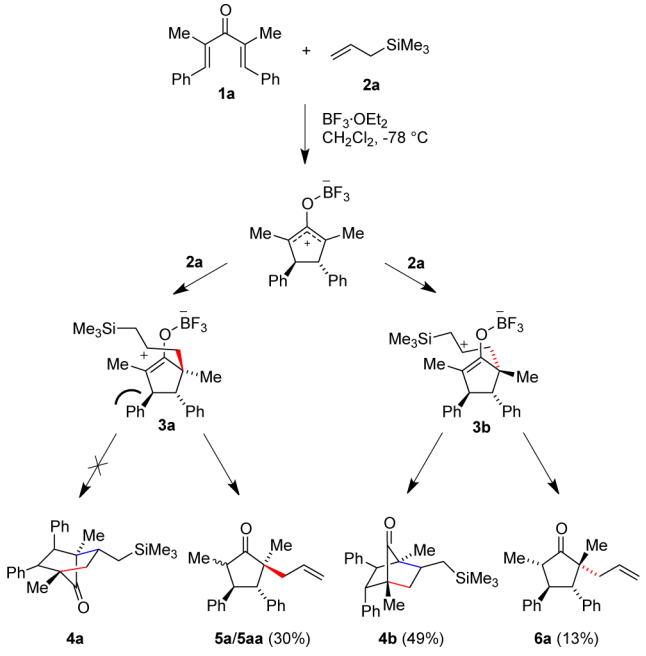
Received: July 26, 2014
Published: September 26, 2014

   dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903−14911

RESULTS AND DISCUSSION

Hosomi−Sakurai-Type Trapping of the Nazarov Intermediate. Our laboratory reported the first use of an intermolecular carbon-based trap, namely, allylsilanes, to capture the cyclized oxyallyl cation in the context of the "interrupted Nazarov" reaction.[11] Initial experiments employing divinyl ketone **1a** and allyltrimethylsilane **2a** in the presence of $BF_3{\cdot}OEt_2$ resulted in the formation of bicyclo[2.2.1]cycloheptanone **4b** as a major constituent along with a diastereomeric mixture of α-allylated cyclopentanones **5a**/**5aa**/**6a** in a combined yield of 43% (Scheme 2).

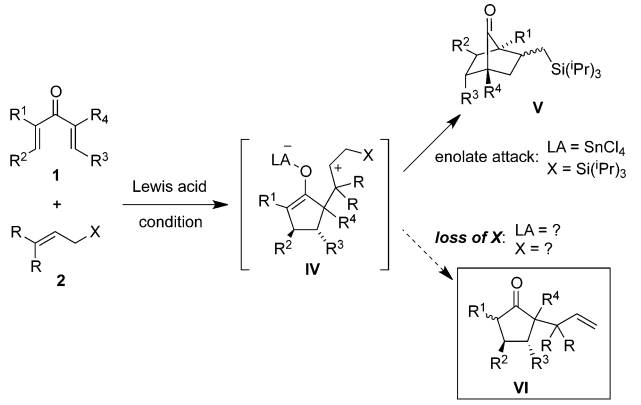
Scheme 2. Divergent Reaction Pathway



Other than simple allylated products, none of **4a** derived from putative intermediate **3a** was detected, likely because repulsive nonbonded interactions exerted from *syn*-phenyl ring hampered the ring closure pathway. On the other hand, zwitterion **3b**, which was formed by the allylsilane attacking from the same face as the adjacent phenyl group, primarily underwent cyclization, yielding bridged bicyclic product **4b**.[12] Besides the occurrence of competing reaction pathways, the diastereofacial selectivity of the nucleophilic attack by **2a** on the 2-oxidocyclopentenyl cation was modest; this ultimately led to minimal selectivity in product formation. However, failure to observe any product arising from either conventional Nazarov cyclization of **1a** or premature Hosomi−Sakurai reaction[13] of **2a** with **1a** is especially promising for applying this chemistry in a broader context.

Alternatively, the use of the more robust allyltriisopropylsilane in the $SnCl_4$-mediated reaction with several dienones led to exclusive generation of bridged bicycles **V** in good yields (Scheme 3). Having bulky substituents on the silicon atom evidently suppressed the desilylation process of intermediate **IV**. Although **V** represents an unusual structure type, we envisioned that 2-allylcyclopentanones would be more versatile synthetic building blocks in the construction of other targets.[14] Therefore, we attempted to identify an ideal allyl donor as well as Lewis acid-initiator that would facilitate the transformation from **IV** to the allylated product **VI** through facile loss of "X" as the termination step. In the present study, we have also unequivocally assigned the relative configuration of **6a** based on X-ray diffraction analysis.

Scheme 3. Elusive Conditions for Complete Selectivity over Umpolung Allylation Pathway

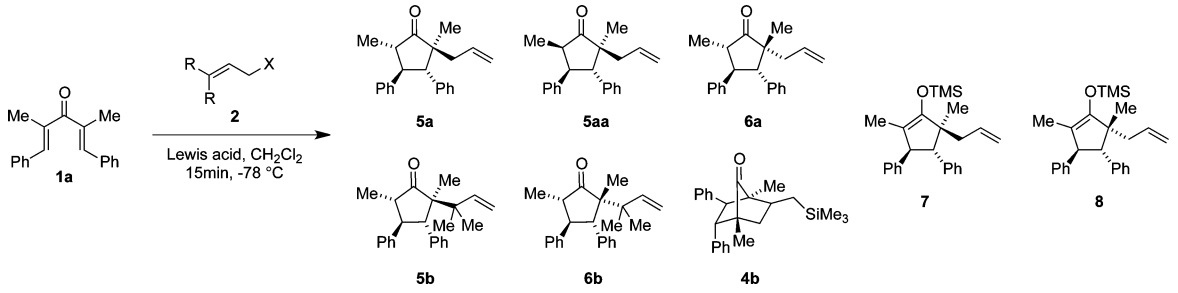


We commenced determination of the optimal Lewis acids for promoting the domino electrocyclization/Hosomi−Sakurai-type allylation process using dienone **1a** (Table 1, entries 1−5). When $SnCl_4$ was employed, a similar product distribution as in the case of $BF_3{\cdot}OEt_2$ was found with diminished overall yield. With TMSOTf, the diastereofacial selectivity was significantly increased, although the undesired [3 + 2] cycloaddition could not be suppressed. To our delight, utilization of $TiCl_4$, a conventional activator for the purpose of the Hosomi−Sakurai reaction, exclusively furnished the allylation products **5a** and **6a** with good diastereofacial control. With precedents of halide transfer from titanium Lewis acids during the Nazarov cyclization,[6a] we presumed that the available chloride species could promote the allylation process by scavenging silylium ions. The effect of Brønsted acid was also investigated in order to discern whether or not protonated oxyallyl species would perform differently from the Lewis acid-bound counterparts. For the model reaction employing **1a** and **2a**, the use of triflic acid, a commonly available superacid, gave inferior chemo- and stereoselectivity.

Next, we turned our focus to the survey of allyl donors possessing different X groups (see **2**) in the interrupted Nazarov reactions. Although boron-based reagents such as **2b** and **2c** are widely used in several types of allylation processes,[15] reaction of **1a** with either allylB(pin) or allyl trifluoroborate salt offered intractable material at the expense of the dienone substrate. Switching to allylstannane **2d**, which is more nucleophilic[16] than allylsilane **2a** yet shares similar stability under Lewis acidic conditions, we found that its reaction with **1a** in the presence of $BF_3{\cdot}OEt_2$ gave a pair of diastereomers **5a** and **6a** with no trace amount of tin-substituted [3 + 2] adducts being formed (entry 1 vs entry 8). This experiment indicated that the loss of the tributyltin moiety following allylstannane addition to the Nazarov intermediate (intermediate **IV**, X = $SnBu_3$) occurred rapidly in analogy to the Keck-type allylation.[17] With that encouraging result in hand, $TiCl_4$ was then employed as the Lewis acid, as it gave an excellent reaction profile in the previous example using allylsilane as the trapping agent. While the yield for $TiCl_4$-mediated reaction of **1a** and **2d** was improved (entry 8 vs entry 9), the diastereofacial selectivity surprisingly remained low. Interestingly, cyclization of **1a** under treatment with **2d** and TMSOTf gave a diastereomeric mixture (ca. 1:5) of TMS-capped products **7** and **8** in 82% combined yield. Trimethylsilyl enol ethers **7** and **8** displayed notable hydrolytic resistance toward the typical workup procedure and silica gel chromatography; the same product type was not detected to

dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903−14911

Table 1. Survey of the Variations of Allyl Donors 2 and Lewis Acids[a]

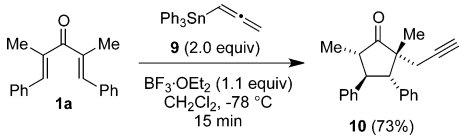


entry	allyl donor **2**, X/R	Lewis acid	allylated products	[3 + 2] adducts	ratio of products[b]	diastereofacial selectivity	combined yield (%)[c]
1	**2a**, $SiMe_3$/H	$BF_3{\cdot}OEt_2$	**5a**/**5aa**/**6a**	**4b**	2:1:1:5	1:2	92
2	**2a**, $SiMe_3$/H	$SnCl_4$	**5a**/**5aa**/**6a**	**4b**	2:1:1:4	1:1.7	58
3	**2a**, $SiMe_3$/H	TMSOTf	**5a**/**6a**	**4b**	1:5:4	1:9	ND[e]
4	**2a**, $SiMe_3$/H	$TiCl_4$	**5a**/**6a**	–	1:9	1:9	90
5	**2a**, $SiMe_3$/H	TfOH	**5a**/**6a**	**4b**	1:2:2	1:4	ND[e]
6	**2b**, B(pin)/H	TMSOTf	–	–	n/a	n/a	n/a
7	**2c**, BF_3K/H	$TiCl_4$	–	–	n/a	n/a	n/a
8	**2d**, $SnBu_3$/H	$BF_3{\cdot}OEt_2$	**5a**/**6a**	–	1:2	1:2	30
9	**2d**, $SnBu_3$/H	$TiCl_4$	**5a**/**6a**	–	1:3	1:3	76
10	**2d**, $SnBu_3$/H	TMSOTf	**7**/**8**	–	1:5	1:5	82
11[d]	**2d**, $SnBu_3$/H	TMSOTf	**5a**/**6a**	–	1:5	1:5	81
12[d]	**2e**, $SnBu_3$/Me	TMSOTf	**5b**/**6b**	–	1:1	1:1	95

[a]Standard procedure: To a stirred solution of dienone **1a** and **2** (2 equiv) in CH_2Cl_2 (0.2 M in **1**) at −78 °C was added Lewis acid (1.1 equiv). After 15 min, the reaction mixture was quenched with sat. aq $NaHCO_3$, followed by extraction with CH_2Cl_2, drying over $MgSO_4$, and chromatographic purification. [b]Determined by integration of ^1H NMR signals of the methyl group at the α-quaternary center. [c]Isolated yield. [d]The reaction was quenched with TsOH instead of sat. aq $NaHCO_3$. [e]ND = Not determined.

any extent in related interrupted Nazarov reactions using other carbon traps together with TMSOTf (vide infra). Significantly, the synthetic potential of this process lies in the fact that compounds **7** and **8** preserved enol-type reactivity of the post-Nazarov intermediate, thus permitting subsequent introduction of electrophiles at the α'-carbon.[18] We are currently examining the viability of interrupting Nazarov reactions sequentially with nucleophiles and electrophiles in a one-pot fashion. Preliminary studies showed that the reaction could be quenched with the simplest electrophile, a proton from TsOH, releasing homoallyl ketones **5a** and **6a** in one pot (entry 11). Use of the more sterically demanding 3,3-disubstituted stannane **2e** furnished the analogous prenylated products **5b** and **6b** in surprisingly good yields, generating contiguous all-carbon quaternary centers (entry 12).

We have described that variation of Lewis acids and/or allyl sources has a dramatic impact on the reaction pathway and product distribution. Selective production of either α-allylated cyclopentanones or [3 + 2] adducts[11] could be achieved; however, there are still demands for further improvement on diastereofacial selectivity of the allylation process. Inspired by the preliminary results with allylic tin traps, we examined the use of allenyl tin species in the model reaction of substrate **1a** (eq 1).[19] We discovered that allenylstannane **9** served as a competent propargyl donor yielding a novel interrupted Nazarov product **10** in good yield. It is noteworthy that the propargylation occurred with a high level of diastereoselectivity, wherein **10** was formed as a single isomer.



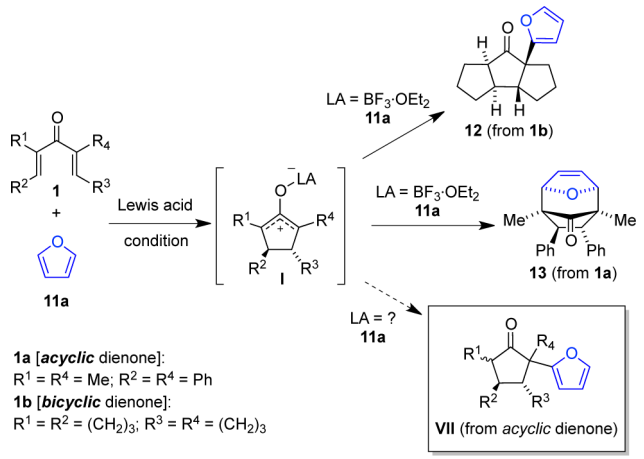
(1)

Friedel–Crafts Trapping of the Nazarov Intermediate with Heterocycles. Oxyallyl cations have emerged as practical three-carbon units in cycloaddition processes.[20] We previously described a reaction in which acyclic divinyl ketone **1a** and furan react in the presence $BF_3{\cdot}OEt_2$ to give keto-bridged cycloadduct **13** exclusively through a domino electrocyclization/[4 + 3]-cycloaddition sequence (Scheme 4).[21] In contrast to that, upon treatment with $BF_3{\cdot}OEt_2$, bis(cyclopentenyl) ketone **1b** underwent Nazarov cyclization and Friedel–Crafts-type reaction, with furan offering α-furyl triquinane **12** in good yield and excellent diastereoselectivity (Scheme 4).[22] Rieder et al. attributed the distinct reactivity of **1a** and **1b** with furan to the conformational effects associated with the Nazarov intermediate. More specifically, the oxyallyl species derived from **1b** may not be able to undergo [4 + 3]-cycloaddition owing to severe steric demands likely encountered toward the formation of polycyclic keto-bridged skeleton. Also, simple eliminative termination leading to conventional Nazarov products may be impeded as a result of diminished conformational mobility in the tricyclic framework; thus, the cationic intermediate may persist long enough to be intercepted by intermolecular arene traps. Accordingly, electrophilic aromatic substitution with furan was the only operative pathway in the case of **1b**.

We considered introduction of a heteroaryl functionality α to a ketone to be a highly valuable transformation.[23] In line with the theme for this paper, we questioned whether or not the scope of umpolung Friedel–Crafts trapping seen with **1b**, whose alkene groups are constrained in a ring, could be extended to simple *acyclic* dienones so a wider range of α-heteroaryl cyclopentanones **VII** could be prepared via a general interrupted Nazarov strategy (Scheme 4).[24] Cramer and Barrows have noted that the electrophilicity of oxyallyl cations, dictated by the degree of covalency between acid center and oxygen

dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903−14911

Scheme 4. Elusive Conditions for Complete Selectivity over Umpolung Heteroarylation Pathway of Acyclic Dienone Precursors

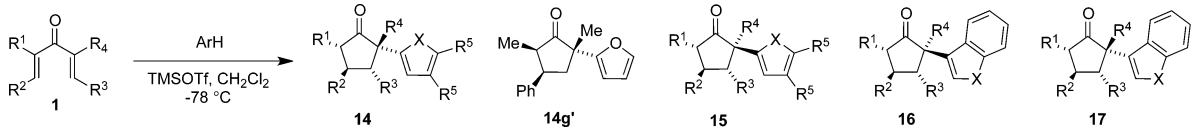


atom, has direct impact on the course of reaction with 1,3-butadiene, wherein increasing electrophilic character associated with the oxyallyl species would promote a stepwise bond-forming mechanism.[25] Inspired by their computational studies, we imagined that, by employing a suitable Lewis acid, electrophilic aromatic substitution of furan with acyclic dienone (e.g., **1a**) could be a dominant pathway, followed by loss of a proton to yield furylation products **VII**, in lieu of structures such as **13**. Indeed, we found that dienone **1a** and furan reacted in the presence of TMSOTf to give one main adduct **14a**, and no keto-bridged product **13** of [4 + 3] cycloaddition was observed. Later, the structure of **14a** (formed as a single diastereomer) was confirmed through single crystal X-ray diffraction analysis. Notably, the 2-furyl substituent α to the cyclopentanone carbonyl group was installed *syn* to the adjacent phenyl ring.

With the new scenario disclosed, we proceeded to examine the generality of this novel α-arylation protocol with other acyclic dienones and heteroaromatic nucleophiles (Table 2). When dienone **1a** was treated with disubstituted furan **11b**, the desired product **14b** was obtained in good yield. Trapping of **1a** with 1-methylpyrrole (**11c**) was very efficient, but the diastereofacial selectivity was modest. On the other hand, no nucleophilic capture was observed with thiophene or benzofuran (entries 4 and 5). Three unsymmetrically substituted dienones **1c,d,e** were also studied in order to probe the regiocontrol of this process (entries 6–9). A high level of regioselectivity was seen in each case providing α-(2-furyl) cyclopentanone in moderate to good yields.[26] Interestingly, 1D NOESY analysis of the products derived from divinyl ketone **1c** suggested all-*trans* stereochemistry for **15d** and **15e** (entries 6 and 7); based on other trapping examples (e.g., **14a**), we had expected predominant or exclusive attack *syn* to the adjacent phenyl substituent. We attributed the reversed facial selectivity to the degree of substitution of the Nazarov oxyallyl; this could be an important factor in its electrophilicity and reactivity.

Application of this reaction to indoles under similar conditions was examined (Table 2, entries 10–15).[27] The TMSOTf-mediated reaction of **1a** and indole **11f** provided the diastereomeric trapped products **16a** and **17a** (ca. 7:1) together with several unidentifiable compounds. We envisioned that utilization of protected indoles as the trapping agents may offer cleaner reaction profiles. As such, tosylindole **11g** was examined, and we later concluded that it was an incompetent nucleophile, excluding further investigations into the use of electron-withdrawing protecting groups. Treatment of **1a** with methylindole **11h** in the presence of TMSOTf gave **16b** and **17b** in a 4:3 ratio, where the diastereofacial selectivity of indole attack was unexpectedly low. However, interruption of the Nazarov cyclization of **1a** with benzylindole **11i** took place efficiently, furnishing a single interrupted Nazarov product, the structure of which was confirmed

Table 2. Domino Electrocyclization/Friedel–Crafts-Type Reaction Sequences[a]



entry	dienone	R^1	R^2	R^3	R^4	ArH	X	R^5	products (yield %)[b]
1	**1a**	Me	Ph	Ph	Me	furan (**11a**)	O	H	**14a** (58)
2	**1a**	Me	Ph	Ph	Me	2,3-dimethylfuran (**11b**)	O	Me	**14b** (90)
3	**1a**	Me	Ph	Ph	Me	1-methylpyrrole (**11c**)	NMe	H	**14c**/**15c** (98; 3:1)[c]
4	**1a**	Me	Ph	Ph	Me	thiophene (**11d**)	S	H	intractable material
5	**1a**	Me	Ph	Ph	Me	benzofuran (**11e**)	O	n/a	intractable material
6	**1c**	Me	Ph	Ph	H	furan (**11a**)	O	H	**15d** (69)
7	**1c**	Me	Ph	Ph	H	2,3-dimethylfuran (**11b**)	O	Me	**15e** (39)
8	**1d**	^{n}Pr	Ph	Ph	Me	furan (**11a**)	O	H	**14f** (66)
9	**1e**	Me	Ph	H	Me	furan (**11a**)	O	H	**14g**/**14g′** (61; 3:1)[c]
10	**1a**	Me	Ph	Ph	Me	indole (**11f**)	NH	n/a	**16a** (48)/**17a** (7)
11	**1a**	Me	Ph	Ph	Me	1-tosylindole (**11g**)	NTs	n/a	intractable material
12	**1a**	Me	Ph	Ph	Me	1-methylindole (**11h**)	NMe	n/a	**16b** (40)/**17b** (32)
13	**1a**	Me	Ph	Ph	Me	1-benzylindole (**11i**)	NBn	n/a	**16c** (92)
14	**1d**	^{n}Pr	Ph	Ph	Me	1-benzylindole (**11i**)	NBn	n/a	**16d** (83)
15	**1e**	Me	Ph	H	Me	1-benzylindole (**11i**)	NBn	n/a	**17e** (74)

[a]Standard procedure: TMSOTf (1.1 equiv) was added to a solution of dienone **1** and heteroarene trap (2 equiv) in CH_2Cl_2 (0.05 M in **1**) at −78 °C. Once the dienone was completely consumed according to TLC analysis (generally less than 30 min), the reaction was quenched with sat. aq $NaHCO_3$, followed by extraction, drying ($MgSO_4$), and chromatographic purification. [b]Isolated yield. [c]Inseparable mixture; the ratio was determined by integration of ^{1}H NMR signals of the methyl group at the α-quaternary center.

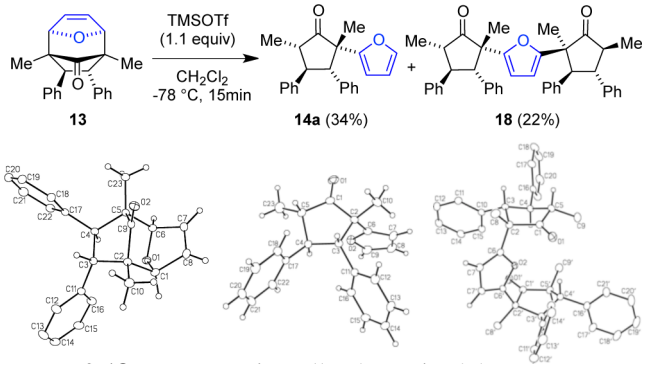
dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903–14911

by X-ray diffraction analysis. The relative stereochemistry of **16c** indicated that **11i** approached *anti* to the adjacent phenyl substituent. The stereochemical outcome is in close analogy to the cases using enol-type traps but is opposed to cases using furans.[9a] We empirically identified **11i** as a more effective indole donor in this process and applied it in the reaction of other dienone substrates. With **1d**, indole-trapped product **16d** was produced in good yield and regioselectivity. Employing the less substituted dienone **1e**, the formation of **17e** was highly selective, as the site and face for trapping were less sterically encumbered.

As noted in the previous studies by our laboratories,[22] arene capture of the Nazarov intermediate derived from bicyclic ketone **1b** with thiophene (**11d**) was exceptionally effective. However, the reactions of acyclic dienone **1a** with **11d** gave intractable material. The absence of any arylation product was disappointing and prompted us to reconsider whether or not the process truly involves a Friedel–Crafts-type mechanism. In the case of **1a** with furan, one may presume that inceptive formation of [4 + 3] adduct **13** was followed by an acid-mediated ring cleavage[28] in a highly stereoselective fashion, to yield furyl cyclopentanones **14a**. Hence, failure to see any trapping event with **11d** might be attributed to two factors: (1) thiophene, possessing higher degree of aromaticity relative to furan and pyrrole,[29] was an incompatible reaction partner in the dearomative cycloaddtion process, and/or (2) the oxyallyl cation derived from the acyclic dienone did not persist long enough to undergo intermolecular Friedel–Crafts trapping.

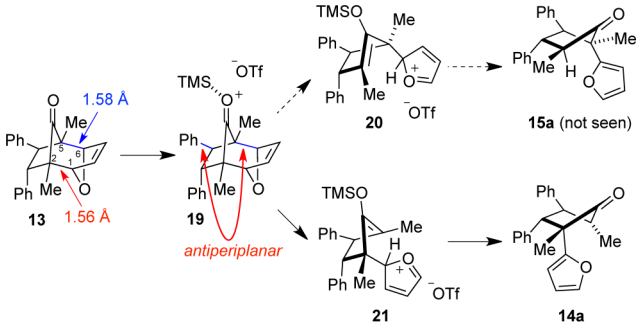
To gain more insight into that, we first prepared the [4 + 3] adduct **13** following the procedure reported by Wang et al.[21] and fortuitously verified its structural assignment by single crystal X-ray diffraction analysis. When we treated compound **13** with the optimized α-arylation conditions (TMSOTf at −78 °C, 15 min), **13** was completely consumed, and **14a** was isolated in 34% yield along with an unusual product **18** having two cyclopentanyl moieties linked through the 2- and 5-positions of the furan ring (Scheme 5). The structural assignment of **18** was

Scheme 5. Mechanistic Studies and ORTEP Drawings of 13, 14a, and 18



unequivocally determined based on X-ray diffraction analysis, which clearly showed the *C*2-symmetry of **18**. It is noteworthy that Grob-type fragmentation of TMS-bound complex **19** only produced intermediate **21**, where the carbon–carbon bond antiperiplanar to the phenyl substitution was selectively cleaved (Scheme 6). This remarkable selectivity may be attributed to subtle stereoelectronic effects imposed by the *exo*-phenyl group.[30] The bond-weakening effect is supported by crystallographic data

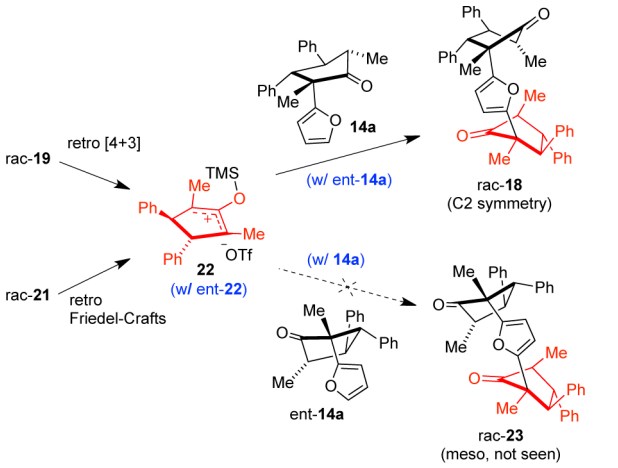
Scheme 6. Formation of 14a via Highly Selective Fragmentation Reaction



of compound **13**, in that the interatomic distance of C5–C6 (1.58 Å) is longer than the one of C1–C2 (1.56 Å).

As for the formation of **18**, we hypothesized that silyloxyallyl cation **22** may arise from either **19** via a retro-[4 + 3] cycloaddition or **21** via a retro-Friedel–Crafts reaction, where the furyl moiety formally serves as a carbon-based leaving group;[31] subsequently, intermediate **22** could be captured by the furan of ring-opened product **14a**, providing *C*2-symmetrical bis(cyclopentanyl) furan **18** (Scheme 7). The identification of

Scheme 7. Proposed Mechanism for the Formation of 18



compound **18** implied that the [4 + 3] cycloaddition reaction of furan and the oxyallyl cation is essentially reversible under specific Lewis acid activation. More intriguingly, the fact that we could not detect any meso isomer **19** implied the occurrence of matched/mismatched interactions between enantiomers of racemate **14a** and rac-intermediate **22**. Overall, we experimentally realized that [4 + 3] adduct **13** could be an intermediary species for the furylation process giving **14a**.

DFT Studies of the Interrupted Nazarov Reaction with Furan. With experimental data in hand, further computational investigations were performed to shed light on the mechanistic details for the apparent domino electrocyclization/Friedel–Crafts reaction sequence. In particular, we sought to understand why the furan was installed *syn* to the phenyl ring in the parent reaction (Table 2, entry 1) and to rationalize the Lewis acid dependent reaction course of the interrupted Nazarov reaction with furan.

Eight potential transition structures were computed for single bond formation between furan and the TMS-activated oxyallyl cation (Figure 1) as well as the BF_3-activated oxyallyl cation

dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903–14911

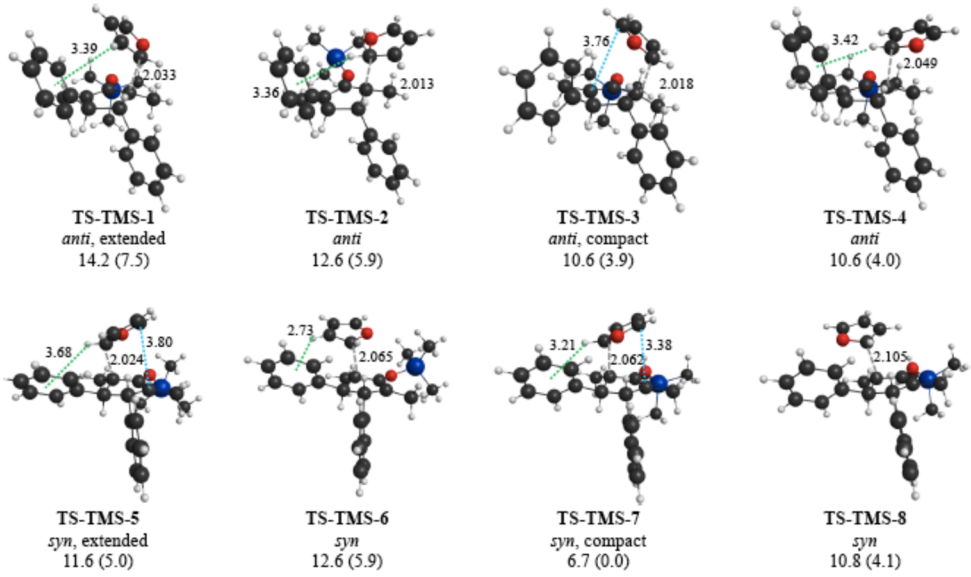


Figure 1. B3LYP/6-311+G(d,p) gas phase geometries of the eight isomeric transition states of furan capture of the oxyallyl cation activated by TMS. Values in parentheses are relative energies in kcal/mol obtained from single point energies in M06-2X/6-311+G(d,p)/PCM(CH_2Cl_2) with thermal contributions to the Gibbs free energy from the gas phase B3LYP/6-311+G(d,p) calculations. Indicated distances are in angstroms.

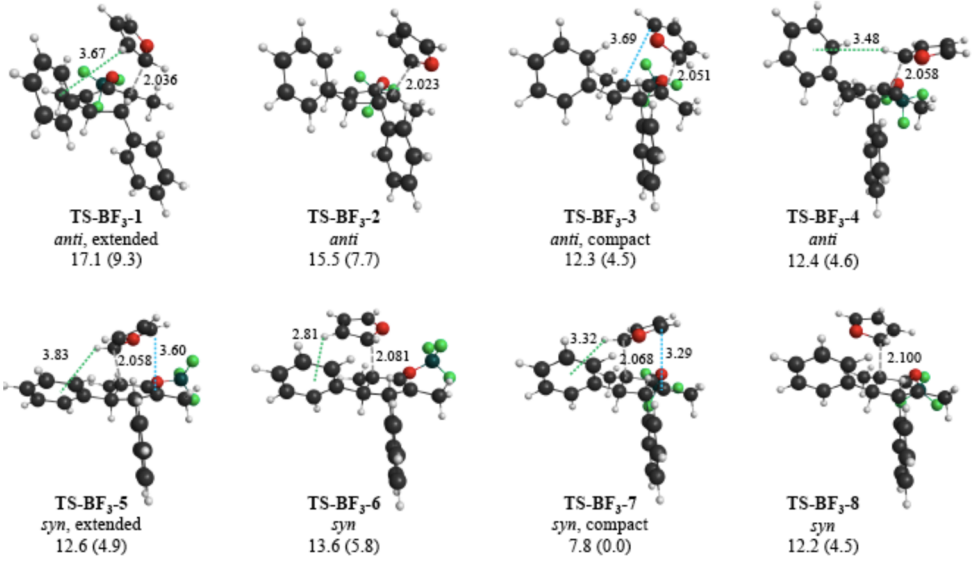


Figure 2. B3LYP/6-311+G(d,p)/PCM(CH_2Cl_2) geometries of the eight isomeric transition states of furan capture of the oxyallyl cation activated by BF_3. Values in parentheses are relative energies in kcal/mol obtained from single point energies in M06-2X/6-311+G(d,p)/PCM(CH_2Cl_2) with thermal contributions to the Gibbs free energy from the B3LYP/6-311+G(d,p)/PCM(CH_2Cl_2) calculations. Indicated distances are in angstroms.

(Figure 2). The compact transition states (**TS-TMS-3,7** and **TS-BF_3-3,7**) are favored over the extended transition states (**TS-TMS-1,5** and **TS-BF_3-1,5**) by 3.6−5.0 kcal/mol, due to enhanced electrostatic interactions.[32] In our case, we also have a steric component due to the adjacent phenyl ring that disfavors the extended transition state. Between two possible compact transition structures, addition *syn* to the adjacent phenyl (**TS-TMS-7**) is favored over *anti* addition (**TS-TMS-3**) by at least 3.9 kcal/mol in the TMS-activated system and 4.5 kcal/mol in the BF_3-activated system (**TS-BF_3-3** versus **TS-BF_3-7**). The computed results of the TMS-activated transition structures are in accordance with the selectivity seen experimentally (Table 2, entry 1). This may be attributed to favorable CH−π interactions between the hydrogen on the 2-position of furan and the overall π system of the neighboring phenyl ring.[33] In **TS-TMS-7**, the hydrogen attached to the carbon on the furan that is undergoing bond formation is 3.21 Å from the center of the adjacent phenyl ring. Though this distance is longer than the typical sp^2 CH−π interaction, which Nishio states to be 2.73 Å ± 0.13,[34] Houk has reported examples as long as 3.2 Å.[35] Additionally, it can be noted that, at the B3LYP/6-311+G(d,p)/PCM(CH_2Cl_2) level, this transition state is only favored by 2.0 kcal/mol. Because M06-2X models dispersion more accurately,[36] it is likely that the extra 1.9 kcal/mol stability of the *syn* transition state using this functional for single point energy calculations is at least partially due to dispersion in the form of the CH−π interaction. Moreover, Houk has reported CH−π interactions in similar reactions between furan and an acyclic oxyallyl cation.[37] In addition to the absence of a CH−π interaction, the *anti* transition structure (**TS-TMS-3**) may be disfavored due to torsional interactions

dx.doi.org/10.1021/ja507638r | J. Am. Chem. Soc. 2014, 136, 14903−14911

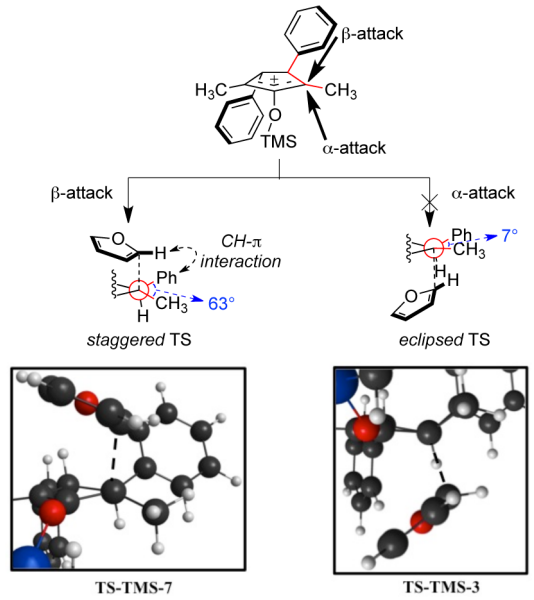


Figure 3. Diastereoselectivity of furan addition dictated by torsional strain and aromatic interactions. Only fractions of **TS-TMS-7** and **TS-TMS-3** are presented for clarity.

between the adjacent phenyl and methyl groups as the furan approaches (Figure 3). In contrast to **TS-TMS-3**, which exhibits substantial eclipsing strain, the *syn* addition of furan leads to a considerably more staggered transition structure (**TS-TMS-7**). The phenomenon of torsional steering has been well-documented in the literature.[38]

Notably, no concerted [4 + 3] transition states could be found in our DFT studies. Previous work by Cramer and Barrows indicate that more electrophilic oxyallyl cations are more likely to undergo stepwise [3 + 2] and [4 + 3] cycloadditions.[25] Additionally, Pérez et al. have shown that 5-membered heterocycles like furan and *N*-methylpyrrole are more likely to undergo Diels–Alder reactions in a stepwise fashion in comparison to cyclopentadiene, which preferentially undergoes concerted Diels–Alder reactions.[39] In fact, Pérez shows competing mechanisms between cycloaddition and electrophilic aromatic substitution (monoaddition) for furan and *N*-methylpyrrole, which is exactly what we see in our interrupted Nazarov reactions. Fernández and Cossío et al. have also reported a stepwise mechanism for an intramolecular [4 + 3] cycloaddition between an oxyallyl and tethered furan.[40]

Computed intermediates and transition structures en route to [4 + 3] cycloadduct and Friedel–Crafts product, mediated by $BF_3{\cdot}OEt_2$ and TMSOTf, respectively, were studied (Figures 4 and 5).[41] Since we were unable to locate transition structures for the concerted [4 + 3] pathway, we propose a stepwise bond-forming mechanism to account for the generation of the adduct **13**. The reaction course diverges after the first bond-forming event between Nazarov oxyallyl and furan. The reaction with $BF_3{\cdot}OEt_2$ favors cycloaddition; as seen in Figure 5, the formation of the second bond to produce the cycloadduct is an exergonic process in addition to having a lower activation barrier than the first bond formation. Although the BF_3-complexed Friedel–Crafts product is lower in energy, this product is not seen in the reaction, presumably because this reaction is kinetically controlled.[42] This is in contrast to the TMSOTf-mediated reaction (Figure 4), in which formation of the cycloadduct is an unfavorable process, being endergonic and kinetically inaccessible. In fact, this explains why the cycloadduct "reverses" to the Friedel–Crafts product when exposed to TMSOTf. Given the structural similarity of TS-TMS-7″ and TS-BF_3-7″, we attributed the drastic difference of activation barrier to the greater unfavorable steric interactions exerted by the trimethylsilyl group as compared with the trifluoroboron group toward the formation of Lewis acid-complexed cycloadducts. In addition, frontier molecular orbital (FMO) analysis of the ring closure event revealed that bonding interactions between the two carbons are significant in TS-BF_3-7″ but, interestingly, not in TS-TMS-7″.[43] While we have shown that [4 + 3] adduct could be the precursor for the furylation product in the presence of TMSOTf (Scheme 5), the computational results (Figure 5) clearly disputed that possibility

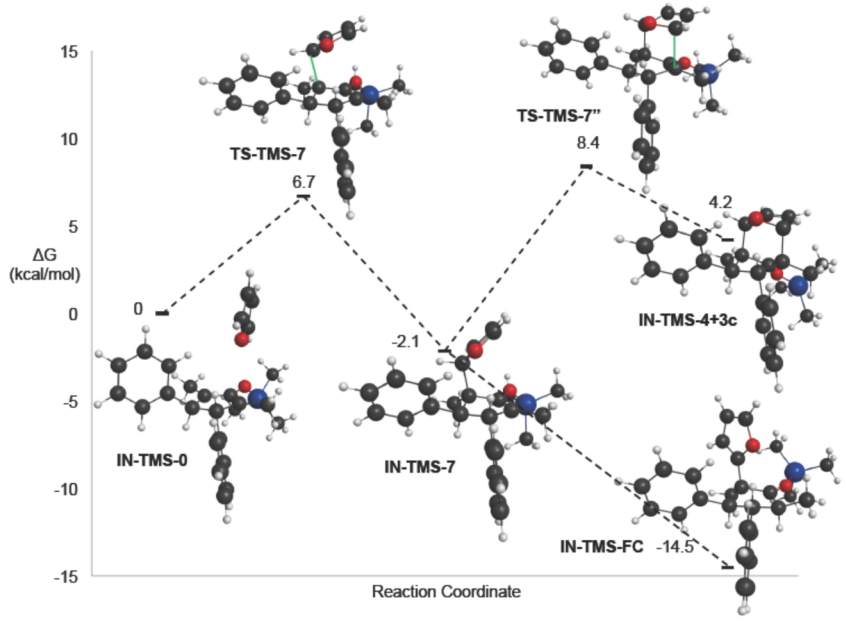


Figure 4. Stationary points in the reaction of TMS-activated oxyallyl cation with furan.

dx.doi.org/10.1021/ja507638r | *J. Am. Chem. Soc.* 2014, 136, 14903–14911

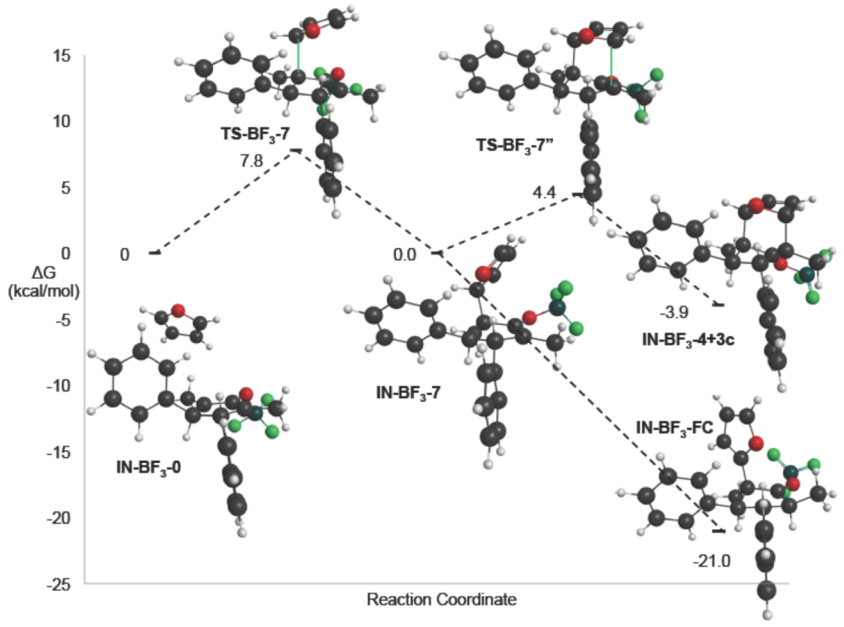


Figure 5. Stationary points in the reaction of BF_3-activated oxyallyl cation with furan.

and presented a comprehensive rationale for the observed pattern of reactivity and stereoselectivity.

CONCLUSIONS

We have described a modular synthetic approach toward α-functionalized cyclopentanoid products in which a variety of structurally simple dienones and easily accessible carbon nucleophiles, such as allylsilane, allylstannane, allenylstannane, and heterocycles, were assembled via interrupted Nazarov chemistry. We see strong evidence that entry into either the cycloaddition or nucleophilic trapping manifolds is governed by both the Lewis acid activator and the nucleophilicity of the trap. Mechanistically, the domino reaction sequence starts with an electrocyclic ring closure of the dienone, giving a stereo-defined cyclopentenyl cation that is then attacked by the π-traps on one terminus of the oxyallyl intermediate, furnishing densely substituted cyclopentanones with the establishment of up to four new stereocenters. In terms of diastereofacial selectivity, the major products observed in the cases using allyl silanes, allylstannanes, pyrroles, and furans as traps predominantly resulted from nucleophilic addition *syn* to the phenyl substituent at the adjacent β-position, but opposite selectivity was seen with examples using indole derivatives. The origins of the high level of diastereoselectivity found in one case with furan as the trapping agent were investigated by DFT methods. Minimal activation energy was required when furan approached the Nazarov oxyallyl cation in a compact fashion. More significantly, we revealed that both torsional steering and CH$-\pi$ interactions played pivotal roles in directing the installation of the furyl moiety *syn* to the adjacent phenyl substituent. Additionally, computational data supports the divergence in reactivity of oxyallyl cations based on the identity of the Lewis acid activator; the formation of the second bond to furnish the cycloadduct is kinetically favored in the BF_3-mediated reaction but disfavored in the TMS-mediated reaction. Echoing the computational findings, the formal [4 + 3] adduct was stereoselectively converted to the α-furylated cyclopentanone and an intriguing 2,5-disubstituted furan upon treatment with TMSOTf. Overall, we showed that the Nazarov reaction, beyond its conventional practice, serves as an initiator for umpolung bond-forming processes. Ongoing research in our laboratory is directed at the development of novel domino reaction sequences initiated by the Nazarov cyclization; also, we would like to continue our *in silico* survey in other interrupted Nazarov pathways.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, ORTEP structures, copies of ^1H and ^{13}C NMR spectra, computational details, and crystallographic information in CIF format. 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.

ACKNOWLEDGMENTS

This work was generously supported by NSERC. Y.K.W. gratefully thanks the Alberta Innovates-Technology Futures for a PhD graduate scholarship and the University of Alberta for a Dissertation Fellowship. C.R.D. thanks NSERC for a Postgraduate Scholarship − Doctoral and the University of Alberta for a Queen Elizabeth II Graduate Scholarship. The authors thank Professor Christopher Cramer, Department of Chemistry, University of Minnesota, for helpful discussions.

REFERENCES

(1) For recent reviews, see: (a) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Vol. 5, Elsevier: Oxford, 2014; pp 827−866. (b) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979−3002. (c) Spencer, W. T.; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, 3621−3633. (d) Shimada, N.; Stewart, C.; Tius, M. A. *Tetradedron* **2011**, *67*, 5851−5870. (e) Vaidya, T.; Eisenberg, R.; Frontier, A. J.

ChemCatChem. **2011**, *3*, 1531−1548. (f) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732−751.
(2) For a review, see: Grant, T. N.; Reider, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676−5688.
(3) Marx, V. M.; Stoddard, R. L.; Heverly−Coulson, G. S.; Burnell, D. J. *Chem.—Eur. J.* **2011**, *17*, 8098−8104.
(4) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685−1689.
(5) Mahmound, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091−5094.
(6) (a) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629−5632. (b) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213−7216.
(7) (a) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472−12473. (b) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256−7257. (c) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019−12022. (d) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703−706.
(8) (a) Marx, V. M.; Burnell, D. J. *Org. Lett.* **2009**, *11*, 1229−1231. (b) Kobubo, M.; Kobayashi, S. *Chem.—Asian J.* **2009**, *4*, 526−528. (c) Shindo, M.; Yaji, K.; Kita, T.; Shishido, K. *Synlett* **2007**, 1096−1100. (d) Yaji, K.; Shindo, M. *Synlett* **2009**, 2524−2528.
(9) (a) Wu, Y.-K.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584−3587. (b) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8616−8619. (c) Kwon, Y.; Scadeng, O.; McDonald, R.; West, F. G. *Chem. Commun.* **2014**, *50*, 5558−5560. (d) Wu, Y.-K.; West, F. G. *Org. Lett.* **2014**, *16*, 2534−2537.
(10) For a review on umpolung reactions at the α-carbon of carbonyl compounds: Miyata, O.; Miyoshi, T.; Ueda, M. *Arkivoc* **2013**, *(ii)*, 60−81.
(11) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970−1973.
(12) For a review on cycloadditions of allylsilanes: Schmidt, A. W.; Knölker, H.-J. *Synlett* **2010**, 2207−2239 and references therein.
(13) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835−851.
(14) For other recent reports on synthesis of homoallyl carbonyls using allylsilanes: (a) Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 1470−1473. (b) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20648−20651. (c) Huang, Y.-t.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536−6550.
(15) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990−998.
(16) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.
(17) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268.
(18) Selected recent examples of interrupting the Nazarov cyclization with electrophiles: (a) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053−3056. (b) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. *Adv. Synth. Catal.* **2009**, *351*, 123−128. (c) Hutson, G. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 4988−4991.
(19) Gung, B. W. *Org. React.* **2004**, *64*, 1−113.
(20) For leading reviews: (a) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904−8922. (b) Harmata, M. *Chem. Commun.* **2010**, *46*, 8886−8903. (c) Lohse, A. G.; Hsung, R. P. *Chem.—Eur. J.* **2011**, *17*, 3812−3822.
(21) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750.
(22) (a) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572−1574. (b) Rieder, C. J.; Fradette, R. J.; West, F. G. *Heterocycles* **2010**, *80*, 1413−1427.
(23) For recent reviews on metal-catalyzed α-arylation with aryl halides, see: (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676−707. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082−1146.
(24) For synthesis of α-aryl ketones employing umpolung strategies, see: (a) Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951−1960. (b) Miyoshi, T.; Miyakawa, T.; Ueda, M.; Miyata, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 928−931. (c) Miyoshi, T.; Sato, S.; Tanaka, H.; Hasegawa, C.; Ueda, M.; Miyata, O. *Tetrahedron Lett.* **2012**, *53*, 4188−4191. (d) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546−4547. (e) Laloo, B. M.; Mecadon, H.; Rohman, Md. R.; Kharbangar, I.; Kharkongor, I.; Rajbangshi, M.; Nongkhlaw, R.; Myrboh, B. *J. Org. Chem.* **2012**, *77*, 707−712. (f) Smith, A. G.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 1784−1787. (g) Redden, A.; Moeller, K. D. *Org. Lett.* **2011**, *13*, 1678−1681. (h) Sperry, J. B.; Wright, D. L. *Tetrahedron* **2006**, *62*, 6551−6557. (i) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857−12869.
(25) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176−186.
(26) **14g′** could be converted into **14g** in the presence of a catalytic amount of DBU.
(27) For intercepting oxyallyl cations with indoles, see: (a) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073−4076. (b) Marx, V. M.; Lefort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2011**, *353*, 64−68. (c) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 1922−1925. (d) Lai, P.-S.; Dubland, J. A.; Sarwar, M. G.; Chudzinski, M. G.; Taylor, M. S. *Tetrahedron* **2011**, *67*, 7586−7592. (e) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075−3079. (f) Li, H.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2014**, *136*, 6288−6296. (g) See also ref 23b.
(28) (a) Cramer, N.; Juretschke, J.; Laschat, S.; Baro, A.; Frey, W. *Eur. J. Org. Chem.* **2004**, 1397−1400. (b) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275−1278. (c) Mann, J.; Wilde, P. D.; Finch, M. W. *Tetrahedron* **1987**, *43*, 5431−5441. (d) Gao, X.; Harmata, M. *Tetrahedron* **2013**, *69*, 7675−7682.
(29) Horner, K. E.; Karadakov, P. B. *J. Org. Chem.* **2013**, *78*, 8037−8043.
(30) Deslongchamp, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.
(31) Williams, Y. D.; Meck, C.; Mohd, N.; Murelli, R. P. *J. Org. Chem.* **2013**, *78*, 11707−11713.
(32) (a) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 819−835. (b) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−88. (c) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523−5532.
(33) For a recent account discussing stereoselectivity of reactions controlled by aromatic rings: Krenske, E. H.; Houk, K. N. *Acc. Chem. Res.* **2013**, *46*, 979−989.
(34) Nishio, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873−13900.
(35) Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749−2752.
(36) Zhao, Y.; Truhlar, D. G. *Chem. Phys. Lett.* **2011**, *502*, 1−13.
(37) Antoline, J. E.; Krenske, E. H.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2011**, *133*, 14443−14451.
(38) For a recent mini review concerning this effect: Wang, H.; Houk, K. N. *Chem. Sci.* **2014**, *5*, 462−470.
(39) Domingo, L. R.; Pérez, P.; Ortega, D. E. *J. Org. Chem.* **2013**, *78*, 2462−2471.
(40) Fernández, I.; Cossío, F. P.; de Cozár, A.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2010**, *16*, 12147−12157.
(41) Alternative reaction pathways were also examined; those results are enclosed in the Supporting Information.
(42) For both Lewis acid cases, the transition states leading to Lewis acid-bound Friedel−Crafts products **IN-TMS-FC** and **IN-BF_3-FC** via proton-transfer were not examined due to the ambiguity of the identity of the proton-abstracting agents.
(43) See the Supporting Information for details.