JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# Domino Acylation/Diels–Alder Synthesis of *N*-Alkyl-octahydroisoquinolin-1-one-8-carboxylic Acids under Low-Solvent Conditions

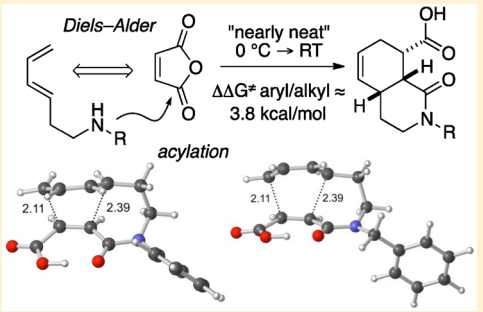
Stephen R. Slauson,[†,§] Ryan Pemberton,[‡] Partha Ghosh,[†,∥] Dean J. Tantillo,[‡] and Jeffrey Aubé*[,†]

[†]Department of Medicinal Chemistry, University of Kansas, Delbert M. Shankel Structural Biology Center, 2034 Becker Drive, Lawrence, Kansas 66047, United States

[‡]Department of Chemistry, University of California at Davis, Davis, California 95616, United States

Supporting Information

**ABSTRACT:** The development of the domino reaction between an aminoethyl-substituted diene and maleic anhydride to afford an N-substituted octahydroisoquinolin-1-one is described. A typical procedure involves the treatment of a 1-aminoethyl-substituted butadiene with maleic anhydride at 0 °C to room temperature for 20 min under low-solvent conditions, which affords a series of isoquinolinone carboxylic acids in moderate to excellent yields. NMR monitoring suggested that the reaction proceeded via an initial acylation step followed by an intramolecular Diels–Alder reaction. For the latter step, a significant rate difference was observed depending on whether the amino group was substituted by a phenyl or an alkyl (usually benzyl) substituent, with the former noted by NMR to be substantially slower. The Diels–Alder step was studied by density functional theory (DFT) methods, leading to the conclusion that the degree of preorganization in the starting acylated intermediate had the largest effect on the reaction barriers. In addition, the effect of electronics on the aromatic ring in *N*-phenyl substrates was studied computationally and experimentally. Overall, this protocol proved considerably more amenable to scale up compared to earlier methods by eliminating the requirement of microwave batch chemistry for this reaction as well as significantly reducing the quantity of solvent.




## INTRODUCTION

Domino reactions involving sequential chemical transformations without the isolation of intermediates permit the quick assembly of complex molecular frameworks,[1] often utilizing the Diels–Alder (DA) reaction as a key component.[2] Although the phrase "domino reaction" did not appear in the chemical literature until 1973,[3] a combined Diels–Alder/acylation reaction of maleic anhydride toward *N*-alkyl-octahydroisoquinolin-1-one-8-carboxylic acids **2** and related heterocycles was first reported in 1968[4] and further developed by other laboratories (see discussion to follow). In 2007, we utilized this sequence to construct a small library of amides derived from **2** (Scheme 1)[5] and subsequently showed that numerous amides containing this scaffold were potent and selective kappa opioid receptor (KOR) binders,[6] notably including some KOR ligands found to be substantially biased for activation of the G-protein signaling pathway relative to $\beta$ arrestin signaling.[7] Because of our current interest in discerning the molecular basis behind such functional selectivity and to utilize molecules derived from **2** as molecular probes, we have used this chemistry to prepare hundreds of isoquinolinone-based KOR agonists.[8]

To facilitate these efforts, we found it desirable to further develop the reaction. In particular, the necessity for microwave conditions in reactions involving nonfuran-based dienes severely limited our ability to scale the reaction up to multigram quantities. In this article, we report that carrying out the reaction under low-solvent conditions allows a practical reduction in reaction temperature from 165 °C to ≤0 °C with a commensurate increase in scalability. Under these new conditions, we also discovered a profound dependence of rate upon the nature of the N-substituent (aryl vs alkyl) and report a combined experimental and theoretical mechanistic study of this effect.

## BACKGROUND

This sequence leverages reactivity inherent in maleic anhydride (MA), a remarkable molecule in that all four carbons in it are sites for reaction. Thus, not only is MA an iconic Diels–Alder dienophile, both ends of the electron-poor double bond are additionally activated toward conjugate addition by nucleophiles, and as an anhydride, it is also subject to nucleophilic acylation. Beginning in the 1960s, a number of workers have explored sequences involving the ready acylation of amines or alcohols by MA to prepare substrates for intramolecular Diels–

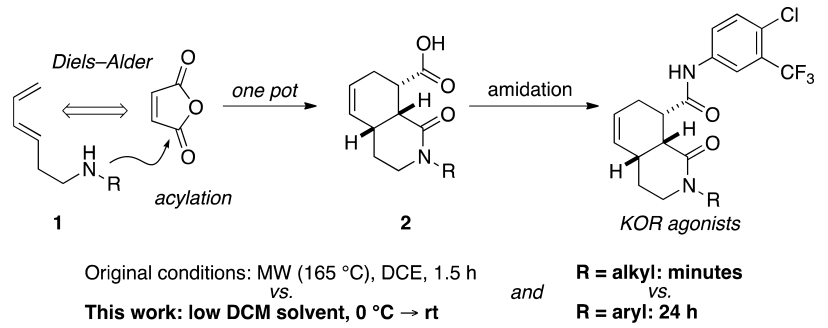
Received: April 10, 2015





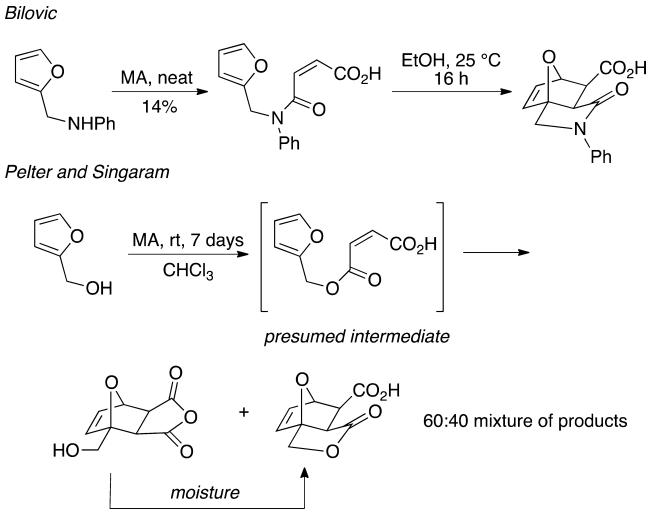
DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX–XXX

**Scheme 1**




Alder reactions, most commonly involving furan as the diene component (Scheme 2). In an instructive early example (1968),

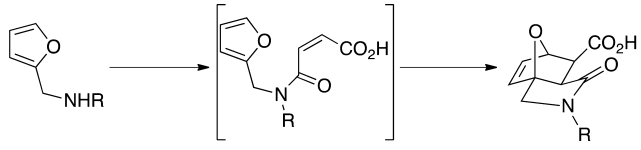
**Scheme 2**




Bilovic described how reacting MA with 2-(aminomethyl)furan resulted in a reaction of the nucleophilic amine with the anhydride moiety of MA, albeit in low yield.[4] Subsequent dissolution of this adduct in EtOH occasioned a Diels–Alder cycloaddition at room temperature over 16 h. In the early 1980s, Pelter and Singaram reported similar chemistry of the corresponding furanyl alcohol, including the observation of the domino Diels–Alder/acylation product under certain circumstances.[9] Although mixtures of anhydride and lactonic acid were obtained as shown, these authors considered the formation of the latter to be the result of an intramolecular Diels–Alder process following initial acylation (supported by a demonstration of cycloaddition of the independently prepared ester, shown in brackets). Nearly simultaneously, Imagawa reported similar results, with a point of particular interest to the present work being that "if the amount of the solvent was exceedingly minimized" the domino reaction product was accompanied by uncycloadded crystalline esterification product, which did not undergo further reaction in the solid state.[10,11]The reaction was even adapted for an undergraduate laboratory experience by McDaniel and Weekly.[12]

A series of papers by Zylber and co-workers focused on the domino amidation/DA chemistry of 2-aminoethyl furans and clarified the mechanistic course of the reactions (Scheme 3).[13] They found the reaction to reliably and efficiently afford the domino amidation/DA product under a variety of conditions,

**Scheme 3**

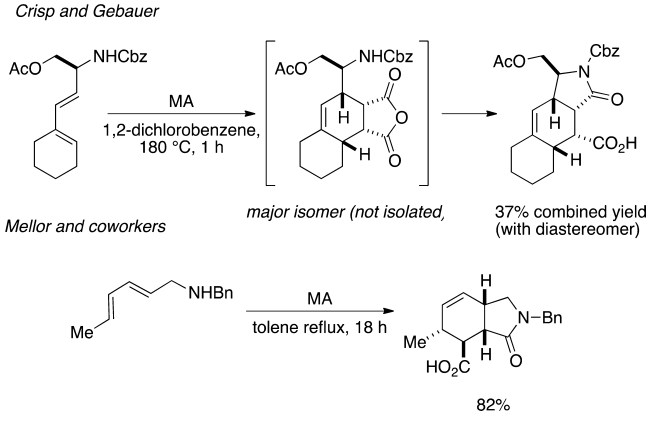


| R | conditions | results |
|---|---|---|
| *i*-Pr | no solvent, rt | • 93% of domino adduct,"in a few minutes" |
| *i*-Pr | in acetone, $CHCl_3$, PhMe, $Et_2O$, or EtOAc, rt | • domino adduct as only product but in 65% yield<br>• unable to detect intermediate |
| Ph | in *d*-acetone, *d*-DMSO, or $CDCl_3$, rt | • domino adduct forms within 5-30 min<br>• IR and NMR observation of amide intermediate (brackets) |
| Ph | $Et_2O$, –10 °C | • isolation of amide (brackets) in 80% yield<br>• IMDA of amide occurs in $CDCl_3$ ($t_{1/2}$ = 90 min) |

but qualitatively noted a rate difference between *N*-alkyl-substituted aminomethylfuran and its *N*-aryl counterpart, which took nominally more time to reach completion. Moreover, the Zylber team was able to detect initial amide formation by IR or NMR, also isolating the amide when carrying out the reaction at −10 °C in $Et_2O$. These results strongly supported the order of reaction as amidation and then DA reaction.

Other researchers have employed the furan or the closely related amidation/DA sequence to provide similar products as discussed above,[14] but only a few examples using nonfuranyl aminoalkyl dienes were reported prior to our 2007 paper (Scheme 4).[5] In 1996, Crisp reported a series of domino reactions using a complex diene containing a relatively non-

**Scheme 4**






DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX−XXX

nucleophilic *N*-Cbz substituent, which unsurprisingly proceeded by intermolecular Diels–Alder reaction followed by transamidation.[15] More relevant here are the reactions reported by Mellor of MA with dienes containing hydroxyalkyl[16] or aminoalkyl[17] substituents, respectively. The example shown in Scheme 4, in which the reaction was carried out in refluxing toluene is typical, although a couple of examples were also reported to give comparable results at 0 °C or rt when dichloro- or dibromomaleic anhydrides, respectively, were used. Finally, White has reported a related isoquinolinone synthesis in which the main event is an innovative diene formation via alkene dehydrogenation, followed by Diels–Alder and transamidation to afford the final products.[18] The utility of the Diels–Alder reaction with downstream[19] or concomitant[20] lactonization reactions has been well noted.

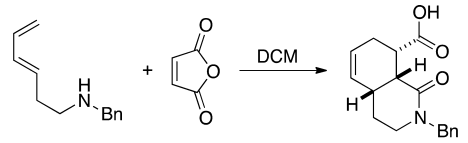
## RESULTS AND DISCUSSION

**Method Development.** The body of work described above clearly established the potential of a combined MA acylation event with the powerful Diels–Alder reaction for the rapid assembly of useful heterocyclic scaffolds. We were especially attracted to this particular reaction sequence in the context of diversity-oriented synthesis because of its modularity (potentially wide choice of diene, if practical, and MA derivatives), easy diversification of the resulting carboxylic acid, and the superficial similarity of the products to turn mimetics (a useful overview and entry into this vast literature has recently appeared[21]). As noted above, our hopes that a library based on this scaffold would prove useful were subsequently realized,[6,7,22] reinforcing our commitment to increasing the suitability of this reaction to routine laboratory use. In this regard, a key bottleneck was the need for carrying out the reaction in a microwave apparatus under high temperature: in our initial article,[5] we reported carrying out the Diels–Alder/acylation sequence of diene **1a** with MA for 1.5 h at 165 °C in dichloroethane (DCE; 0.4 M in **1a**). Moreover, the past emphasis on furan dienes suggested that greater exploration of reaction partners would be essential for optimal utility.

A key breakthrough that allowed us to achieve these goals was the observation that an exotherm occurred when the diene and maleic anhydride were combined in the absence of solvent; when the reaction was scaled up to ≥5 mmol, the exotherm was sufficiently strong to necessitate cooling the reaction in ice. Moreover, we noted that the reaction went to completion under these conditions, without the requirement for microwave heating. Accordingly, we sought out conditions for optimizing this low-solvent ("nearly-neat"), non-MW variation as a means of optimizing the reaction for downstream analogue synthesis and preparation of larger quantities of product.

As shown in Table 1, trials with variations in temperature and time led us to optimal conditions that included maintaining an initial reaction temperature of 0 °C for 10 min removal of the cooling bath and allowing for slow warming for an additional 10 min. This protocol resulted in control of the exotherm in addition to providing product in good yield (entries 1–4, 10). Experimenting with the order of addition, maintenance of strictly anhydrous conditions, and varying molar equivalencies of dienophile failed to provide a significant increase in yield (entries 5–6). Since most of the isoquinolinone carboxylic acids were solids, we turned to adding a minimal amount of DCM so as to increase the yield by ensuring complete conversion (entries 7–11; see Table 1 for concentrations). Changes in reaction scale resulted in similar results (entries 12–13). The reaction is highly endoselective, with the exo isomer consistently representing ca. 2–3% of the isolated products.

**Table 1. Optimization of Conditions**




1a 2a

| entry | scale (mmol) | conc (M) | temp (°C)[a] | time (min) | equiv of MA[b] | yield[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 2.5 | 5.0 | rt | 10 | 1.1 | 64[d] |
| 2 | 2.5 | 5.0 | rt | 30 | 1.1 | 61 |
| 3 | 2.5 | 5.0 | A | 20 | 1.1 | 62 |
| 4 | 2.5 | 5.0 | A | 45 | 1.1 | 71 |
| 5 | 2.5 | 5.0 | A | 20 | 1.1 | 63[e] |
| 6 | 2.5 | 5.0 | B | 20 | 2.0 | 72 |
| 7 | 2.5 | 1.25 | B | 20 | 1.1 | 73 |
| 8 | 2.5 | 1.66 | B | 20 | 1.1 | 74 |
| 9 | 2.5 | 2.5 | B | 20 | 1.1 | 77 |
| 10 | 2.5 | 5.0 | B | 20 | 1.1 | 83 |
| 11 | 2.5 | neat | B | 20 | 1.1 | 78[f] |
| 12 | 1.0 | 5.0 | B | 20 | 1.1 | 80 |
| 13 | 5.0 | 5.0 | B | 20 | 1.1 | 75 |

[a]Conditions: A = reagents combined at 0 °C and allowed to warm to rt for the time designated; B = held at 0 °C for 10 min, then allowed to warm from 0 to 25 °C over 10 min. [b]MA = maleic anhydride. [c]Average of three runs, except where otherwise noted. [d]When scaled up to 5 mmol under these conditions, the reaction erupted from the flask. [e]Strictly anhydrous conditions; single run. [f]Solidified during reaction; stirring was stopped.

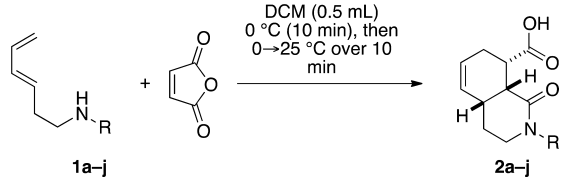
Applying the optimized conditions to a panel of amine dienes, each of which was prepared in four steps from ethyl sorbate using reported methods,[5] provided the desired isoquinolinone products in moderate to excellent yields (Table 2). Benzyl (entry 1) and simple alkyl (entries 3–6) substitutions provided the desired products in good yield. Aryl (entries 2, 7–8) substituents provided good to excellent yields under slightly modified conditions, necessitated by a reduced reaction rate. Addition of an electron-withdrawing group on a diene containing an *N*-benzyl substituent had minimal effect (entry 9), whereas one containing an *N*-allyl substituent provided the desired product in good yield (entry 10). In an extension of our originally reported method, (*E*)-hexa-3,5-dien-1-ol (**1k**), an intermediate in the synthesis of the amine tethered dienes, also provided the corresponding lactone product in good yield (entry 11). All analogues again showed high endo selectivity with exo products being easily separable and accounting for ca. 2–3% of the isolated yield. As discussed above, researchers as early as Bilovic[4] and more comprehensively demonstrated by Zylber[13] had carried out analogous intramolecular Diels–Alder reactions at room temperature with furan-based dienophiles, particularly under neat or highly concentrated conditions; the reaction rate enhancement of the unconstrained dienes examined here through the simple expedient of minimizing solvent is both remarkable and convenient for gram-scale preparation of isoquinolinones **2**.

We also examined examples using citraconic anhydride and phenyl maleic anhydride as dienophiles (Scheme 5). Not surprisingly, the reactions were slower than those observed with maleic anhydride, necessitating higher temperatures for good

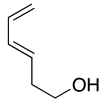
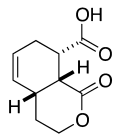


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX–XXX

**Table 2. Reaction Scope**

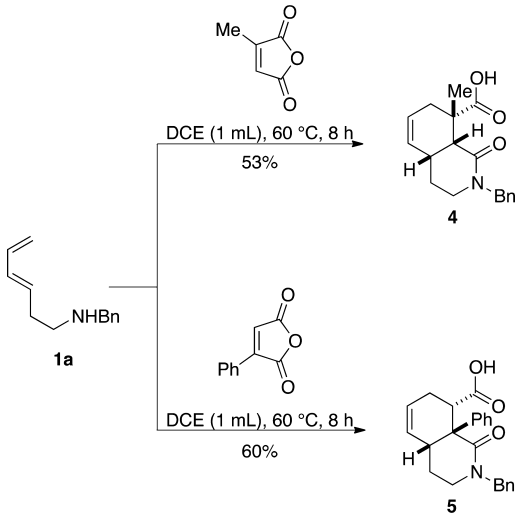



1a–j 2a–j

| entry | series | R | conditions[a] | yield[b] (%) |
|---|---|---|---|---|
| 1 | **a** | $-CH_2Ph$ | A | 83 |
| 2 | **b** | –Ph | B | 70[c] |
| 3 | **c** | $-CH_2$-*c*-$C_6H_{11}$ | A | 76 |
| 4 | **d** | *c*-$C_6H_{11}$ | A | 57 |
| 5 | **e** | *n*-Bu | A | 92 |
| 6 | **f** | *t*-Bu | A | 43 |
| 7 | **g** | *p*-methoxyphenyl | C | 98[c] |
| 8 | **h** | 2,4,6-trimethylphenyl | C | 72[c] |
| 9 | **i** | 2-fluorobenzyl | A | 75 |
| 10 | **j** | allyl | A | 86 |
| 11 |  1k |  2k | D | 81[c] |

[a]Reaction conditions: A: as given above. B: 90 min at 40 °C. C: 120 min at 40 °C. D: 75 min at 25 °C. [b]Average of three runs, except where noted. [c]Results for a single run only.

**Scheme 5**




conversions. After 8 h in minimal dichloroethane (DCE) at 60 °C, a single major product was isolated from each reaction along with small amounts of related material, presumably representing other isomers. The citraconic anhydride reaction provided **4** in 53% yield, while the phenyl maleic anhydride reaction provided the regioisomeric **5** in 60% yield. These results are consistent with literature reports that acylation of citraconic anhydride occurs at the less hindered carbonyl, while attack at the more hindered position is favored for phenylmaleic anhydride.[23] The structures of **4** and **5** were confirmed by X-ray diffraction analysis.

**Mechanistic Observations.** Early attempts to isolate reaction intermediates from reactions carried out under the originally reported conditions (1.5 h, 165 °C, MW)[5] were inconclusive. In most cases, no intermediates were isolated, although at the time we favored a mechanism involving initial Diels–Alder reactions at the high reaction temperatures. In contrast, NMR monitoring of reactions conducted at room temperature in $CDCl_3$ clearly shows that an initial acylation reaction occurs first to provide amido acid **3**, which is then followed by an intramolecular Diels–Alder cycloaddition (Figure 1). The intermediacy of **3** was evident by the observation of downfield-shifted diene protons in a spectrum obtained upon the addition of maleic anhydride to diene **1g** and immediately placing the sample into the spectrometer (Figure 1). This new intermediate was converted to the isoquinolinone product over varying time intervals. This sequence of events is consistent with the mechanism first clearly elucidated by Zylber and colleagues.[13]

We noted an interesting dependence on the rate of the Diels–Alder reaction on the nitrogen substituent of diene **1**, with *N*-alkyl-containing examples being complete within 5–20 min but *N*-aromatic substrates proceeding at a much slower rate. For example, the intermediate arising from *N*-*p*-methoxyphenyl-containing diene **1g** shown in Figure 1 took over 24 h for the disappearance of intermediate **3g** at room temperature. Alternatively, heating at 40 °C for 1.5–2 h was sufficient for the complete conversion of less reactive aryl substrates like **1b**, **1g**, and **1h**. As clearly indicated in Figure 1, the acylation is complete essentially immediately upon addition of the reagents. Nonetheless, to confirm that the observed rate differences could not be due to temperature differences resulting from different exotherms during the acylation step, dienes **1a** (*N*-benzyl) and **1b** (*N*-phenyl) were separately dissolved in $CDCl_3$ (0.41 mmol diene, 0.25 mL $CDCl_3$; this slight dilution of the standard conditions was necessary for NMR lock and shimming at lower temperatures) and kept at −5 °C (see Supporting Information). Maleic anhydride (0.45 mmol) was then added, and reaction monitoring began at −5 °C and continued at 5 min intervals as the reaction was warmed from 0 to 25 °C. Although the MA adduct **3** intermediately formed at −5 °C for both substrates, the *N*-benzyl example **3a** began to convert to product at −5 °C, while the *N*-phenyl analogue **3b** showed no change over this time period. After 2 h


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX–XXX

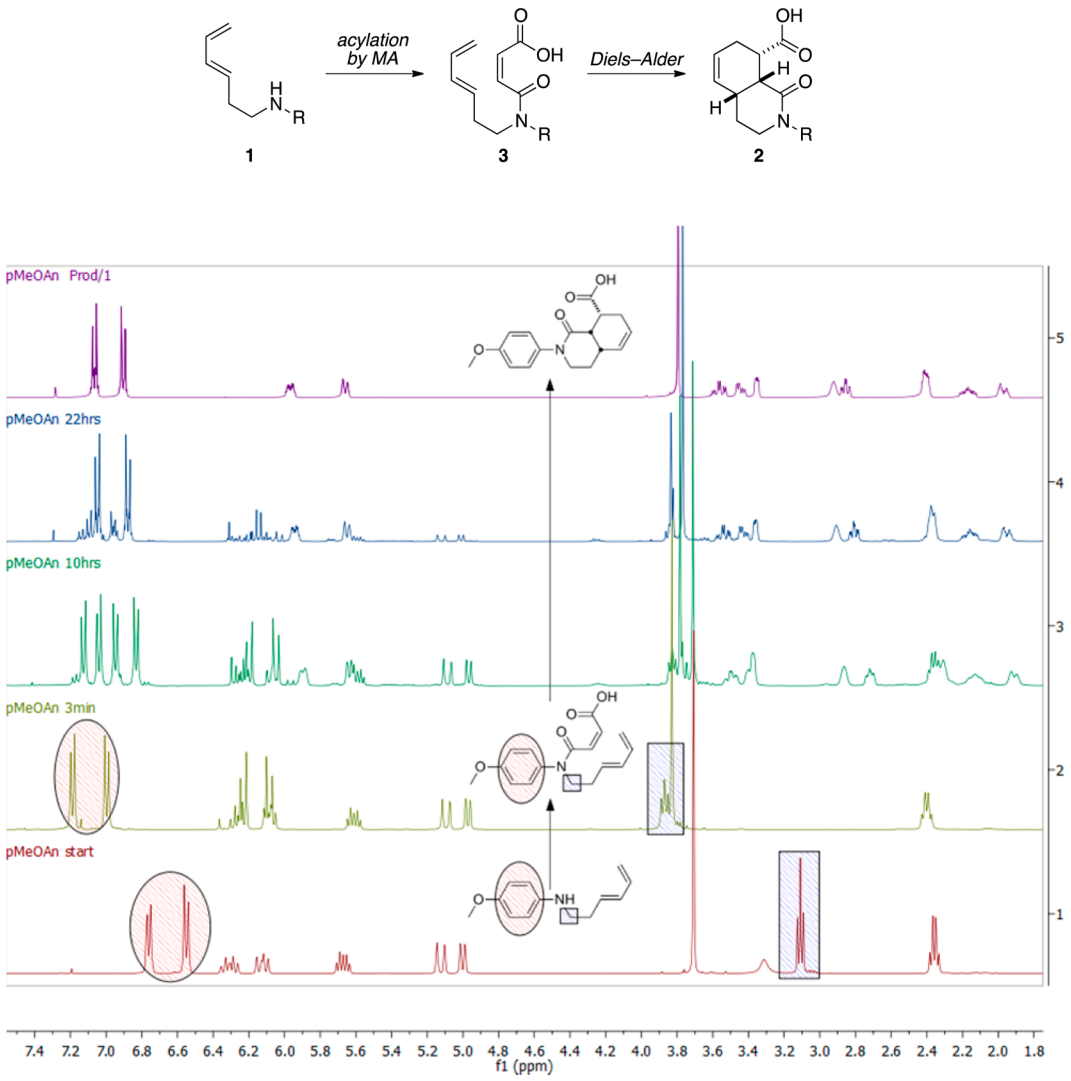



**Figure 1.** NMR monitoring of the reaction of **1g** (where R = *p*-methoxyphenyl) with MA in $CDCl_3$.

at 25 °C, the reaction of **3a** was nearly complete, while **3b** demonstrated limited product formation even after 6 h. Thus, it is clear that the rate differences between the two broad series of substrates arise from a slower Diels–Alder reaction of *N*-aryl than *N*-alkyl amides. Accordingly, we carried out a DFT study of the transition state to determine the molecular features associated with this rate difference.

**Modeling of Transition Structures.** Amides **3a** (*N*-benzyl) and **3b** (*N*-phenyl) were subjected to conformational searching using Spartan 10,[24] and each prospective conformer was optimized with the Merck Molecular Mechanics Force Field (MMFF);[25] conformers with energies greater than 50 kcal/mol above the lowest energy conformer were rejected. The generated MMFF conformers were then optimized at the M06-2X/6-31+G(d,p)[26] level of theory in Gaussian 09.[27] This resulted in six conformers of **3a** within 3 kcal/mol of the lowest energy conformer, but a single conformer of **3b** was found to be >3 kcal/mol lower in energy than all others (only the two lowest-energy conformers, which represent ca. 77% of the overall sample, are discussed in detail below; see Supporting Information for all computed conformers). In addition, transition state conformations **TS1** and **TS2** were generated in a similar manner, with the constraint that the two forming bonds were frozen at 2.20 Å for the MMFF optimizations. This constraint was lifted for the HF/3-21G transition state optimizations and subsequent M06-2X/6-31+G(d,p) transition state optimizations. Frequency calculations were performed on all stationary structures to verify that each was a minimum or transition state structure.

Low energy conformers **3a-A**, **3a-B**, and **3b-B** each contain $\pi$-stacking interactions between the dienophile and the *s-trans*-diene (Figure 2). Conformer **3b-A** lacks this interaction. In this case, the $\pi$-stacking arrangement would incur a steric effect between an *ortho* substituted hydrogen on the *N*-phenyl ring and an internal hydrogen of the diene (while also eclipsing the ethylene tether; top right in Figure 2). Furthermore, the observation that a *cis* relationship of the carbonyl group and the phenyl group only appears in the relatively high-energy (4.8 kcal/mol) conformer **3b-B** highlights an enhanced preference for *N*-aryl-*N*-alkyl substituted amides to adopt a conformation in which the carbonyl and aryl groups are *trans* to one another. Although the conformational preferences of most tertiary amides simply reflect the size differential between the two nitrogen substituents at equilibrium,[28] *N*-aryl-*N*-alkyl acetamides are known to favor the *trans*-aryl conformations at equilibrium.[29] For comparison, *N*-methyl-*N*-phenylformamide was also optimized and favors the isomer where the carbonyl and phenyl are *trans* by 2.3 kcal/mol (Saito calculated a similar


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX−XXX

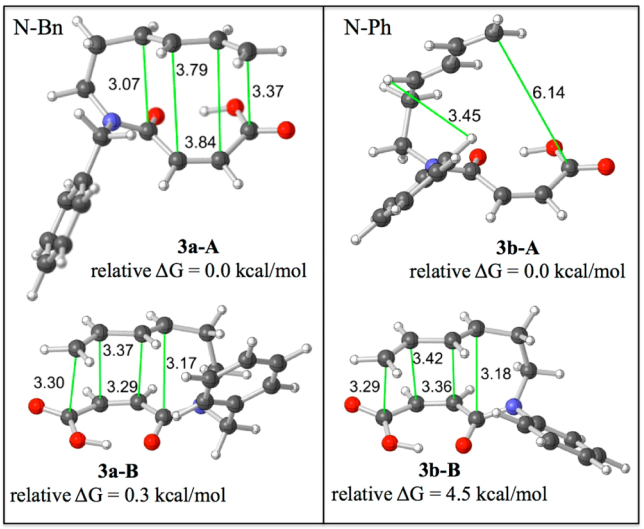



**Figure 2.** Two lowest energy conformers of **3a** and **3b**. Relative free energies shown were calculated using M06-2X/6-31+G(d,p).

preference for *N*-methyl-*N*-phenylacetamide at 3.5 kcal/mol[29a]). Gschwend has discussed the effect of *N*-H vs *N*-alkyl-substituted amide conformations on the rates of intramolecular Diels–Alder reactions,[30] and Mellor reported intramolecular Diels–Alder reactions of both alkyl- and aryl-substituted amides but without commenting on their relative rates.[17] Here, we propose that the relative stability of nonreactive *trans*-aryl conformations could be one factor in slowing the intramolecular Diels–Alder reaction of **3b** relative to **3a**. The consideration of amide bond geometry is related to the observed rate decrease of ester tethered trienes versus their amide counterparts due to preference for the transoid conformer (Table 2, entry 11).[31]

Rotation around the *s-trans* single bond of the diene in both **3a** and **3b** affords the lowest energy Diels–Alder transition state structures for each reaction (Figure 3). Both the *N*-Bn and

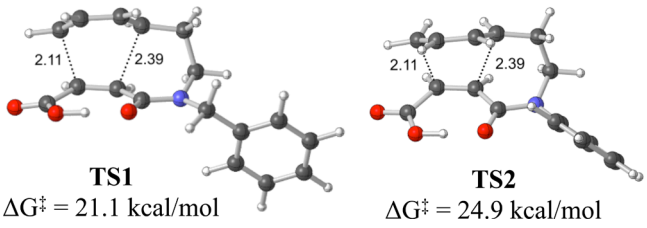



**Figure 3.** Lowest energy transition state structures for the *N*-Bn substituted (**TS1**) and *N*-Ph substituted (**TS2**) reactions. The free energy barriers shown are at the M06-2X/6-31+G(d,p) level relative to reactant conformers **3a-A** and **3b-A**, respectively.

*N*-Ph groups prefer to be *cis* to the carbonyl group to allow the tether to orient the core structure into a conformation productive for cycloaddition. The diene and dienophile adopt the boat transition state geometry associated with transition state structures for concerted Diels–Alder reactions, and the newly formed ring (with the tether) also contains a boat-like geometry.[32] Overall, the $\Delta\Delta G^{\ddagger}$ of 3.8 favoring **TS1** over **TS2** recapitulates the experimental observation of faster Diels–Alder steps for *N*-alkyl vs *N*-aryl amides and, combined with the relatively fast and therefore non-rate-limiting amide formation step in both examples, the overall domino conversion of dienes **1** plus MA to afford isoquinolinones **3**.

$^1$H NMR analyses of the six conformers within 3 kcal/mol of **3a** and conformers **3b-A** and **3b-B** were performed using the linear scaling approach advocated for by Bally and Rablen[33] and Lodewyk et al.[34] The Boltzman-weighted mean absolute deviation (MAD) and the MAD of the lowest energy conformer for the *N*-benzyl system were compared to the experimentally determined $^1$H chemical shifts (see Supporting Information). As expected, the weighted average MAD was less than the MAD of the lowest energy conformer. Additionally, the $^1$H chemical shifts for the lowest energy conformer of both systems matched the experimental spectra best. No weighted average was performed on **3b** since the closest free energy minimum to **3b-A** is **3b-A**, which is 4.8 kcal/mol higher in energy. On the basis of the $^1$H NMR data, it appears that the key to the lower barrier for **TS1** is the conformational preorganization of the reactant, **1**.

**Effect of Aryl Group Substitution.** A series of calculations (vide infra) suggested that *N*-aryl group substitution would have a measurable impact on the relative rates of the intramolecular Diels–Alder reactions. There is limited literature on the effect of aryl substitution of *N*-arylanilides on Diels–Alder kinetics, even when embedded in the common *N*-phenylmaleimide dienophile.[35] We thought this matter of general interest due to the relative distance between the electronically differentiated aryl group and the reactive dienophile.

First, a Hammett-like[36] plot was generated computationally for **TS2** with various *para* substituents on the *N*-phenyl ring (Figure 4). A perfluoronated *N*-phenyl ring was also examined,

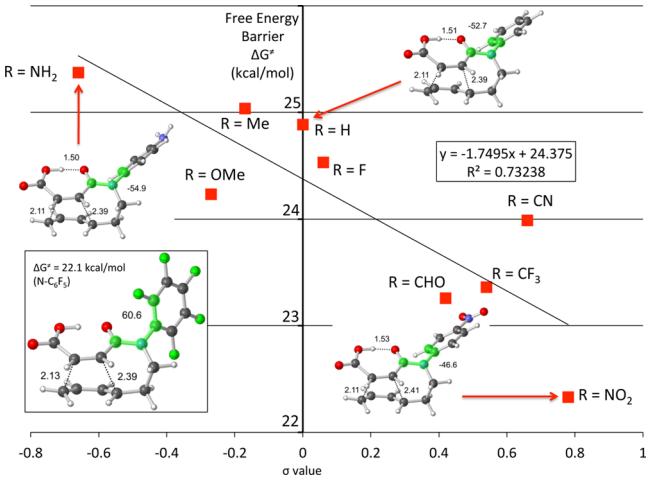



**Figure 4.** Computationally predicted Hammett plot for the reaction proceeding through **TS2**.

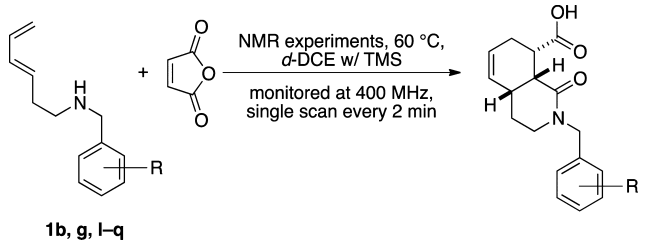
which gave a predicted free-energy barrier of 22.2 kcal/mol. The negative slope of this plot is consistent with a decrease of positive charge increase in the transition state on the dienophile. The slope is small, however, and predicts a relatively small rate enhancement when electron-withdrawing groups are substituted on the *N*-phenyl ring. Interestingly, as the $\sigma$-value increases, so does the overlap of the $\pi$-system of the *N*-phenyl ring with the amide $\pi$-system (see the highlighted dihedral angles in Figure 4).

Additional substituted-aryl substrates were then synthesized to compare to the results suggested through modeling (Table


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX–XXX

3). Although initial qNMR experiments were performed, it was quickly realized that a single scan of the concentrated, nearly

**Table 3. Conversion Times of Substituted *N*-aryl Domino Reactions**




**1b, g, l–q**

| | | time to conversion (min) | | | |
|---|---|---|---|---|---|
| starting material | R | 10% | 25% | 50% | 75% |
| **1l** | *p*-$NMe_2$ | 21 | 53 | 85 | NA[a] |
| **1g** | *p*-OMe | 23 | 53 | 89 | 185 |
| **1m** | *o*-OMe | 11 | 25 | 41 | NA[a] |
| **1n** | *m*-OMe | 9 | 15 | 21 | 35 |
| **1b** | H | 15 | 29 | 49 | NA[a] |
| **1o** | *m*-F | 6 | 9 | 13 | 24 |
| **1p** | *o*-F | <5 | 7 | 11 | 21 |
| **1q** | *p*-F | 6 | 13 | 17 | 28 |

[a]NA: experiment was discontinued before the time point was established.

neat solution without steady state scans provided clear spectra that are quantitative. Direct observation through a NMR time course utilizing a fixed delay between scans provided a reaction profile with data points every 2 min under slightly modified nearly neat conditions (60 °C, *d*-dichloroethane, 1.75M). The reactions were tracked according to percent conversion and the results displayed in Table 3. As shown, the substrates followed the expected distribution with reference to our hypothesis. We note that the *meta*- and *para*-nitro substrates were also attempted but had significant conversion before the load, lock, and shim sequence could be finished (~5 min) and so are not included in Table 3.

## CONCLUSIONS

The combined acylation of amino dienes with MA, followed by an intramolecular Diels–Alder reaction, is a domino sequence of high synthetic potential but one that has only recently been examined outside the specialized use of furan dienes. In this article, we show that carrying out the overall reaction under low-solvent conditions dramatically reduces the temperature needed for synthetically useful conversions and improves the scalability of the process. While low-solvent conditions have obvious value[37] (and have particularly found utility in the many guises of the Diels–Alder reaction[38]), the present work notably demonstrates a clear kinetic advantage of nearly neat conditions over more traditional reaction concentrations and permits us to use extremely simple reaction conditions to provide a valuable class of hetereocycles on a multigram scale.

Examination of the reaction course by NMR supports a mechanism involving a fast, initial acylation reaction followed by a subsequent intramolecular Diels–Alder reaction. This stands in contrast to a domino Diels–Alder/lactonization sequence recently reported by Romo,[20b] in which the Diels–Alder step took the lead, but is consistent with the closely related reactions as elucidated by Zylber.[13] The rate of the cycloaddition step was shown to strongly depend on the nature of the nitrogen atom substituent on the starting amino diene, with *N*-alkyl examples undergoing rapid Diels–Alder reactions and *N*-aryl versions taking much longer to go to completion. DFT studies qualitatively reproduced these results and suggest that the faster *N*-alkyl versions benefit from a greater degree of preorganization in the triene Diels–Alder substrates. Other researchers have noted conformational effects arising from *N*-arylanilide linkers on Diels–Alder,[39] radical,[40] and other[41] reactions, suggesting that our observations may be generalizable to other intramolecular reactions. Finally, we note that a DFT study predicted the dependence of reaction rates on the *N*-phenyl substituent, which was only subsequently confirmed by experiment (a recently published perspective article discusses the upside potential of using theory to inform experimental design[42]).

## EXPERIMENTAL SECTION

**General.** Chemicals were used as received from commercial vendors with no additional purification. (*E*)-*N*-(Hexa-3,5-dien-1-yl)cyclohexanamine (**1d**) and (*E*)-*N*-butylhexa-3,5-dien-1-amine (**1e**) were prepared as previously reported.[5] (*E*)-3,5-Hexadien-1-ol (**1k**) was prepared as reported by Miller and Batey.[43] (*E*)-Hexa-3,5-dien-1-yl methanesulfonate and (*E*)-*N*-benzylhexa-3,5-dien-1-amine (**1a**) were prepared as reported by Plietker et al.[44] "Wet" ether eluent refers to buffered acetic acid ether eluent (9:1:0.1 diethyl ether/0.5 M aqueous $KH_2PO_4$/acetic acid) as reported by Taber et al.[45] Infrared (IR) spectra were acquired from a thin film with absorptions reported in $cm^{-1}$. High-resolution mass spectra (HRMS) were obtained using [$ESI^+$] and TOF. Microwave synthesis experiments were carried out using a Biotage Initiator apparatus with internal temperature detection.

**(*E*)-*N*-Substituted-hexa-3,5-dien-1-amines.** *General Procedure.* (*E*)-Hexa-3,5-dien-1-yl methanesulfonate (22.7 mmol) was added to an oven-dried 20 mL microwave vial. Acetonitrile (4.0 mL) was added, followed by amine (68.2 mmol). The reaction was then capped and heated by microwave to 130 °C for 60 min. The reaction was diluted with 1 N NaOH (75 mL) and extracted with DCM (2 × 75 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The oily residue was purified by chromatography to provide the product.

*(E)-N-Benzylhexa-3,5-dien-1-amine (**1a**).*[44] Light yellow oil; yield 3.74 g (88%); $R_f$ = 0.36 (EtOAc). IR (film): 1582 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38–7.22 (m, 4H), 7.24–7.11 (m, 1H), 6.39–6.16 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.14–5.97 (m, 1H), 5.69–5.55 (dt, $J$ = 15.2, 7.1 Hz, 1H), 5.11–5.00 (d, $J$ = 16.9 Hz, 1H), 5.00–4.84 (d, $J$ = 10.0 Hz, 1H), 3.83–3.66 (s, 2H), 2.71–2.61 (t, $J$ = 6.8 Hz, 2H), 2.33–2.16 (q, $J$ = 6.9 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 140.3, 136.4, 132.7, 132.4, 128.4, 128.1, 126.9, 115.5, 53.9, 48.5, 33.1. HRMS: $m/z$ calcd for $C_{13}H_{18}N$, 188.1439; found, 188.1440.

*(E)-N-(Hexa-3,5-dien-1-yl)aniline (**1b**).*[6] Light red oil; yield 2.51 g (64%); $R_f$ = 0.71 (hexanes/EtOAc, 3:1). IR (film): 1602 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22–7.13 (m, 2H), 6.78–6.66 (tt, $J$ = 7.3, 1.0 Hz, 1H), 6.66–6.56 (m, 2H), 6.43–6.24 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.24–6.08 (m, 1H), 5.80–5.62 (dt, $J$ = 15.1, 7.1 Hz, 1H), 5.22–5.09 (d, $J$ = 16.9 Hz, 1H), 5.09–4.95 (d, $J$ = 10.1 Hz, 1H), 3.82–3.55 (br s, 1H), 3.28–3.16 (t, $J$ = 6.8 Hz, 2H), 2.50–2.35 (q, $J$ = 6.8 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 148.1, 136.8, 133.3, 131.6, 129.3, 117.5, 116.0, 112.9, 43.2, 32.5. HRMS: $m/z$ calcd for $C_{12}H_{16}N$, 174.1283; found, 174.1295.

*(E)-N-(Cyclohexylmethyl)hexa-3,5-dien-1-amine (**1c**).* Orange oil; yield 3.05 g (70%); $R_f$ = 0.45 (MeOH/EtOAc, 1:1). IR (film): 1603 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.39–6.21 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.21–6.00 (m, 1H), 5.77–5.56 (dt, $J$ = 15.1, 7.1 Hz, 1H), 5.17–5.04 (d, $J$ = 18.0 Hz, 1H), 5.04–4.87 (d, $J$ = 10.7 Hz, 1H), 2.72–2.57 (t, $J$ = 7.0 Hz, 2H), 2.48–2.35 (d, $J$ = 6.7 Hz, 2H), 2.34–2.20 (q, $J$ = 6.9 Hz, 2H), 1.76–1.64 (m, 5H), 1.48–1.39 (m, 1H), 1.29–1.10 (m, 4H), 0.94–0.79 (m, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 137.0,


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX–XXX

132.61, 132.55, 115.3, 56.7, 49.4, 38.0, 33.2, 31.5, 26.7, 26.1. HRMS: $m/z$ calcd for $C_{13}H_{24}N$, 194.1908; found, 194.1912.

*(E)-N-(tert-Butyl)hexa-3,5-dien-1-amine (**1f**).* Yellow oil; yield 998 mg (29%); $R_f$ = 0.15 (MeOH/EtOAc, 1:1). IR (film): 1558 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.35−6.26 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.18−6.09 (m, 1H), 5.72−5.60 (dt, $J$ = 15.2, 7.0 Hz, 1H), 5.16−5.07 (d, $J$ = 16.9 Hz, 1H), 5.03−4.95 (d, $J$ = 10.1 Hz, 1H), 2.86−2.78 (br s, 1H), 2.70−2.59 (t, $J$ = 7.2 Hz, 2H), 2.35−2.25 (q, $J$ = 7.2, 1.4 Hz, 2H), 1.18−1.07 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 137.0, 132.8, 132.2, 115.6, 50.9, 41.7, 33.3, 28.6. HRMS: $m/z$ calcd for $C_{10}H_{20}N$, 154.1596; found, 154.1592.

*(E)-N-(Hexa-3,5-dien-1-yl)-4-methoxyaniline (**1g**).* Red oil; yield 2.97 g (64%); $R_f$ = 0.49 (hexanes/EtOAc, 4:1). IR (film): 1602 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.86−6.70 (m, 2H), 6.65−6.51 (m, 2H), 6.43−6.23 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.23−6.05 (m, 1H), 5.78−5.58 (dt, $J$ = 15.1, 7.1 Hz, 1H), 5.23−5.08 (d, $J$ = 18.0 Hz, 1H), 5.08−4.92 (d, $J$ = 10.1 Hz, 1H), 3.83−3.66 (s, 3H), 3.23−3.06 (t, $J$ = 6.7 Hz, 2H), 2.50−2.30 (q, $J$ = 6.7 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 152.2, 142.4, 136.8, 133.2, 131.7, 115.9, 114.9, 114.3, 55.8, 44.2, 32.5. HRMS: $m/z$ calcd for $C_{13}H_{18}NO$, 204.1388; found, 204.1400.

*(E)-N-(Hexa-3,5-dien-1-yl)-2,4,6-trimethylaniline (**1h**).* Light yellow oil; yield 3.95 g (81%); $R_f$ = 0.71 (hexanes/EtOAc, 4:1). IR (film): 1645 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.86−6.73 (s, 2H), 6.44−6.26 (dt, $J$ = 16.8, 10.2 Hz, 1H), 6.26−6.09 (m, 1H), 5.83−5.63 (dt, $J$ = 15.1, 7.2 Hz, 1H), 5.23−5.09 (d, $J$ = 16.9 Hz, 1H), 5.08−4.91 (d, $J$ = 10.1 Hz, 1H), 3.10−2.94 (t, $J$ = 6.8 Hz, 2H), 2.46−2.28 (q, $J$ = 6.9 Hz, 2H), 2.27−2.21 (m, 9H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 136.8, 133.3, 132.0, 131.2, 129.5, 129.4, 115.8, 47.9, 33.9, 20.6, 18.4. HRMS: $m/z$ calcd for $C_{15}H_{22}N$, 216.1752; found, 216.1763.

*(E)-N-(2-Fluorobenzyl)hexa-3,5-dien-1-amine (**1i**).* Yellow oil; yield 3.42 g (73%); $R_f$ = 0.67 (MeOH/EtOAc, 1:1). IR (film): 1632 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.28 (td, $J$ = 7.5, 1.7 Hz, 1H), 7.26−7.16 (m, 1H), 7.14−7.06 (td, $J$ = 7.4, 1.2 Hz, 1H), 7.06−6.92 (m, 1H), 1.54−1.45 (dt, $J$ = 16.9, 10.3 Hz, 1H), 6.40−6.20 (m, 1H), 5.73−5.59 (dt, $J$ = 14.8, 7.1 Hz, 1H), 5.19−5.04 (d, $J$ = 16.64 Hz, 1H), 5.04−4.91 (d, $J$ = 10.1 Hz, 1H), 3.93−3.76 (s, 2H), 2.79−2.61 (t, $J$ = 6.9 Hz, 2H), 2.38−2.20 (q, $J$ = 6.4 Hz, 2H), 1.54−1.42 (br s, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 161.2 (d, $J$ = 244.0 Hz), 137.0, 132.7, 132.3, 130.4 (d, $J$ = 4.9 Hz), 128.6 (d, $J$ = 8.2 Hz), 127.2 (d, $J$ = 15.0 Hz), 124.0 (d, $J$ = 4.0 Hz), 115.5, 115.3 (d, $J$ = 22.0 Hz), 48.4, 47.2 (d, $J$ = 3.0 Hz), 33.1. HRMS: $m/z$ calcd for $C_{13}H_{17}FN$, 206.1345; found, 206.1358.

*(E)-N-Allylhexa-3,5-dien-1-amine (**1j**).* Yellow oil; yield 1.87 g (60%); $R_f$ = 0.23 (MeOH/EtOAc, 1:1). IR (film): 1646 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.43−6.20 (dt, $J$ = 16.9, 10.3 Hz, 1H), 6.20−6.03 (m, 1H), 6.02−5.78 (m, 1H), 5.76−5.57 (dt, $J$ = 15.2, 7.2 Hz, 1H), 5.24−5.04 (m, 3H), 5.04−4.87 (d, $J$ = 10.1 Hz, 1H), 3.33−3.14 (dt, $J$ = 6.0, 1.4 Hz, 2H), 2.76−2.62 (t, $J$ = 6.9 Hz, 2H), 2.38−2.21 (q, $J$ = 6.3 Hz, 2H), 1.44−1.38 (br s, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 136.9, 136.5, 132.8, 132.3, 116.1, 115.5, 52.2, 48.4, 33.0. HRMS: $m/z$ calcd for $C_9H_{16}N$, 138.1283; found, 138.1285.

*(E)-N-(Hexa-3,5-dien-1-yl)-N,N-dimethylbenzene-1,4-diamine (**1l**).* Reddish-brown oil; yield 966 mg (20%); $R_f$ = 0.70 (EtOAc/Hex, 1:1). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.81−6.75 (d, $J$ = 8.8 Hz, 2H), 6.68−6.61 (d, $J$ = 8.3 Hz, 2H), 6.43−6.31 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.24−6.14 (m, 1H), 5.79−5.71 (dt, $J$ = 15.2, 7.1 Hz, 1H), 5.21−5.14 (d, $J$ = 16.9 Hz, 1H), 5.08−5.03 (d, $J$ = 10.1 Hz, 1H), 3.24−3.14 (t, $J$ = 7.0 Hz, 2H), 2.86 (s, 6H), 2.47−2.40 (q, $J$ = 6.9 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 144.2, 140.7, 136.9, 133.1, 131.9, 115.9, 115.8, 114.6, 44.3, 42.3, 32.7. HRMS: $m/z$ calcd for $C_{14}H_{20}N_2$+H, 217.1705; found, 217.1723.

*(E)-N-(Hexa-3,5-dien-1-yl)-2-methoxyaniline (**1m**).* Light yellow oil; yield 1.99 g (58%); $R_f$ = 0.75 (EtOAc/Hex, 1:3). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.95−6.89 (td, $J$ = 7.6, 1.4 Hz, 1H), 6.83−6.79 (dd, $J$ = 8.0, 1.4 Hz, 1H), 6.73−6.65 (m, 2H), 6.44−6.33 (dt, $J$ = 17.2, 10.2 Hz, 1H), 6.26−6.16 (m, 1H), 5.83−5.74 (m, 1H), 5.22−5.16 (d, $J$ = 16.9 Hz, 1H), 5.08−5.04 (d, $J$ = 10.2 Hz, 1H), 4.31−4.22 (br s, 1H), 3.88 (s, 3H), 3.28−3.23 (t, $J$ = 6.9 Hz, 2H), 2.52−2.46 (q, $J$ = 7.0 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 146.9, 138.2, 136.9, 133.0, 131.8, 121.3, 116.5, 115.7, 109.9, 109.5, 55.4, 43.1, 32.5. HRMS: $m/z$ calcd for $C_{13}H_{17}NO$+H, 204.1388; found, 204.1398.

*(E)-N-(Hexa-3,5-dien-1-yl)-3-methoxyaniline (**1n**).* Dark yellow oil; yield 1.54 g (45%); $R_f$ = 0.63 (EtOAc/Hex, 1:3). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.15−7.09 (t, $J$ = 8.1 Hz, 1H), 6.37−6.18 (m, 5H), 5.78−5.70 (m, 1H), 5.23−5.16 (d, $J$ = 16.9 Hz, 1H), 5.10−5.05 (d, $J$ = 10.1 Hz, 1H), 3.81 (s, 3H), 3.77−3.63 (br s, 1H), 3.25−3.20 (t, $J$ = 6.8 Hz, 2H), 2.49−2.42 (q, $J$ = 6.7 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 160.9, 149.6, 136.8, 133.3, 131.6, 130.0, 116.0, 106.1, 102.5, 98.8, 55.1, 43.2, 32.4. HRMS: $m/z$ calcd for $C_{13}H_{17}NO$+H, 204.1388; found, 204.1405.

*(E)-3-Fluoro-N-(hexa-3,5-dien-1-yl)aniline (**1o**).* Yellow oil; yield 1.17 g (36%); $R_f$ = 0.72 (EtOAc/Hex, 1:3). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.15−7.09 (m, 1H), 6.42−6.31 (m, 4H), 6.24−6.16 (m, 1H), 5.78−5.69 (dt, $J$ = 15.2, 7.1 Hz, 1H), 5.24−5.16 (d, $J$ = 17.0 Hz, 1H), 5.11−5.04 (d, $J$ = 10.2 Hz, 1H), 3.87−3.74 (br s, 1H), 3.23−3.17 (t, $J$ = 6.8 Hz, 2H), 2.50−2.42 (q, $J$ = 6.8 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 164.2(d, $J$ = 241.1 Hz), 150.0 (d, $J$ = 10.8 Hz), 136.71, 133.44, 131.24, 130.3 (d, $J$ = 10.3 Hz), 116.16, 108.7 (d, $J$ = 2.3 Hz), 103.7 (d, $J$ = 21.8 Hz), 99.4 (d, $J$ = 25.4 Hz), 43.01, 32.27. HRMS: $m/z$ calcd for $C_{12}H_{14}FN$+H, 192.1189; found, 192.1186.

*(E)-2-Fluoro-N-(hexa-3,5-dien-1-yl)aniline (**1p**).* Yellow oil; yield 1.29 g (40%); $R_f$ = 0.69 (EtOAc:Hex, 1:1). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.06−6.98 (m, 2H), 6.77−6.72 (m, 1H), 6.69−6.63 (m, 1H), 6.43−6.33 (dt, $J$ = 16.9, 10.2 Hz, 1H), 6.26−6.17 (m, 1H), 5.81−5.72 (dt, $J$ = 15.2, 7.1 Hz, 1H), 5.24−5.16 (d, $J$ = 15.0 Hz, 1H), 5.11−5.03 (d, $J$ = 10.2 Hz, 1H), 3.99−3.89 (br s, 1H), 3.30−3.25 (t, $J$ = 6.8 Hz, 2H), 2.52−2.45 (q, $J$ = 6.9 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 151.6 (d, $J$ = 239.2 Hz), 136.8, 136.7 (d, $J$ = 11.6 Hz), 133.4, 131.2, 124.6 (d, $J$ = 3.5 Hz), 116.6 (d, $J$ = 7.0 Hz), 116.1, 114.4 (d, $J$ = 18.5 Hz), 112.1(d, $J$ = 3.4 Hz), 42.9, 32.4. HRMS: $m/z$ calcd for $C_{12}H_{14}FN$+H, 192.1189; found, 192.1187.

*(E)-4-Fluoro-N-(hexa-3,5-dien-1-yl)aniline (**1q**).* Reddish oil; yield 1.92 g (61%); $R_f$ = 0.69 (EtOAc/Hex, 1:3). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.95−6.88 (m, 2H), 6.60−6.55 (m, 2H), 6.43−6.31 (dt, $J$ = 17.2, 10.2 Hz, 1H), 6.24−6.14 (m, 1H), 5.78−5.69 (dt, $J$ = 15.1, 7.2, 1H), 5.23−5.15 (d, $J$ = 17.0 Hz, 1H), 5.09−5.04 (d, $J$ = 10.2 Hz, 1H), 3.65−3.40 (br s, 1H), 3.22−3.16 (t, $J$ = 6.7 Hz, 2H), 2.48−2.41 (q, $J$ = 6.8 Hz, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 155.8 (d, $J$ = 235.6 Hz), 144.5 (d, $J$ = 2.0 Hz), 136.8, 133.4, 131.5, 116.1, 115.8, 115.5, 113.8, 113.7, 43.8, 32.4. HRMS: $m/z$ calcd for $C_{12}H_{14}FN$+H, 192.1189; found, 192.1188.

**2-Substituted-1-oxo-1,2,3,4,4*a*,7,8,8*a*-octahydroisoquinoline-8-carboxylic Acid.** *General Procedures. Conditions A.* The N-substituted amine diene (2.5 mmol) was added to a round-bottomed flask, dissolved in dichloromethane (0.5 mL), and cooled to 0 °C in an ice bath. The maleic anhydride (2.75 mmol, 270 mg) was then weighed and added in one portion to the diene solution. The resulting mixture was maintained at 0 °C for 10 min, then the ice bath was removed and the reaction allowed to warm at room temperature for an additional 10 min. The reaction was then immediately diluted with dichloromethane (2.0 mL) and loaded directly onto a silica gel column. Product isolation occurred by gradient elution with 0−100% hexanes/"wet" ether.

*Conditions B.* The protocol for conditions A was followed, then heated to 40 °C for 90 min.

*Conditions C.* The protocol for conditions A was followed, then heated to 40 °C for 120 min.

*Conditions D.* The protocol for conditions A was followed except that once the ice bath was removed, the reaction was allowed to stir at room temperature for 75 min.

*2-Benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2a**).*[5] Clear crystalline solid; yield 597 mg (84%); Mp 158−161 °C; $R_f$ = 0.46 ("wet" ether). IR (film): 2924, 1703 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.24 (m, 3H), 7.23−7.09 (m, 2H), 5.98−5.77 (m, 1H), 5.67−5.43 (d, $J$ = 10.0 Hz, 1H), 4.79−4.62 (d, $J$ = 14.6 Hz, 1H), 4.58−4.43 (d, $J$ = 14.6 Hz, 1H), 3.31−3.19 (dd, $J$ = 5.6, 2.4 Hz, 1H), 3.19−3.06 (m, 2H), 2.96−2.87 (ddd, $J$ = 11.6, 5.6, 2.5 Hz, 1H), 2.87−2.76 (br s, 1H), 2.53−2.28 (m, 2H), 2.07−1.92 (m, 1H), 1.92−1.80 (dq, $J$ = 14.0, 3.6 Hz, 1H). $^{13}C$ NMR (101 MHz,


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX−XXX

$CDCl_3$) $\delta$ 175.8, 171.9, 135.9, 129.5, 128.7, 127.8, 127.7, 127.5, 51.0, 45.3, 44.0, 41.3, 34.8, 27.0, 25.6. HRMS: $m/z$ calcd for $C_{17}H_{20}NO_3$, 286.1443; found, 286.1466.

*1-Oxo-2-phenyl-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2b**).*[6] White solid; yield 474 mg (70%); Mp 199−204 °C; $R_f$ = 0.45 ("wet" ether). IR (film): 3004, 1702 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.50−7.36 (m, 2H), 7.36−7.28 (tt, $J$ = 7.4, 1.4 Hz, 1H), 7.20−7.05 (m, 2H), 6.06−5.92 (m, 1H), 5.75−5.56 (d, $J$ = 10.0 Hz, 1H), 3.70−3.55 (td, $J$ = 12.6, 4.5 Hz, 1H), 3.55−3.43 (m, 1H), 3.39−3.26 (dd, $J$ = 5.3, 2.4 Hz, 1H), 3.00−2.86 (m, 2H), 2.55−2.37 (m, 2H), 2.25−2.11 (m, 1H), 2.06−1.93 (dtd, $J$ = 13.8, 4.2, 1.9 Hz, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.5, 172.4, 142.1, 129.7, 129.5, 127.8, 127.3, 126.1, 48.4, 45.1, 41.7, 34.8, 27.3, 25.4. HRMS: $m/z$ calcd for $C_{16}H_{18}NO_3$, 272.1287; found, 272.1297.

*2-(Cyclohexylmethyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2c**).* White solid; yield 572 mg (79%); Mp 82−84 °C; $R_f$ = 0.44 ("wet" ether). IR (film): 2923, 1705 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.00−5.80 (m, 1H), 5.66−5.45 (dd, $J$ = 10.0, 1.6 Hz, 1H), 3.50−3.36 (dd, $J$ = 13.3, 8.6 Hz, 1H), 3.36−3.20 (td, $J$ = 12.6, 4.8 Hz, 1H), 3.20−3.08 (m, 2H), 3.08−2.97 (dd, $J$ = 13.3, 6.7 Hz, 1H), 2.97−2.86 (ddd, $J$ = 12.3, 4.8, 2.3 Hz, 1H), 2.86−2.73 (br s, 1H), 2.49−2.37 (m, 1H), 2.37−2.19 (m, 1H), 2.06−1.83 (m, 2H), 1.80−1.48 (m, 6H), 1.24−1.08 (m, 3H), 1.00−0.84 (m, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.5, 172.1, 129.7, 127.5, 54.3, 46.1, 45.2, 40.9, 35.5, 34.8, 30.9, 30.3, 27.1, 26.3, 25.9, 25.74, 25.67. HRMS: $m/z$ calcd for $C_{17}H_{26}NO_3$, 292.1913; found, 292.1935.

*2-Cyclohexyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2d**).*[5] White solid; yield 389 mg (56%); Mp 167−169 °C; $R_f$ = 0.48 ("wet" ether). IR (film): 2927, 1704 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.98−5.76 (m, 1H), 5.64−5.43 (d, $J$ = 9.9 Hz, 1H), 4.53−4.27 (m, 1H), 3.26−3.15 (dt, $J$ = 12.4, 4.0 Hz, 1H), 3.15−2.97 (m, 2H), 2.92−2.81 (ddd, 12.2, 5.1, 2.7 Hz, 1H), 2.81−2.69 (br s, 1H), 2.48−2.19 (m, 2H), 1.93−1.49 (m, 7H), 1.43−1.22 (m, 4H), 1.18−0.89 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 176.1, 171.1, 129.5, 127.2, 53.9, 45.6, 41.4, 38.3, 34.1, 29.5, 29.4, 27.1, 25.63, 25.55, 25.5. HRMS: $m/z$ calcd for $C_{16}H_{24}NO_3$, 278.1756; found, 278.1770.

*2-Butyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2e**).*[5] White solid; yield 593 mg (95%); Mp 122−124 °C; $R_f$ = 0.34 ("wet" ether). IR (film): 2929, 1709 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.85−5.66 (m, 1H), 5.54−5.39 (d, $J$ = 10.0 Hz, 1H), 3.41−3.31 (m, 1H), 3.22−2.96 (m, 4H), 2.77−2.56 (m, 2H), 2.31−2.04 (m, 2H), 1.99−1.67 (m, 2H), 1.46−1.25 (m, 2H), 1.25−1.05 (m, 2H), 0.85−0.66 (t, $J$ = 7.3 Hz, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 176.7, 170.7, 129.1, 127.5, 47.5, 44.3, 44.1, 41.4, 34.5, 28.7, 26.9, 24.9, 19.8, 13.7. HRMS: $m/z$ calcd for $C_{14}H_{22}NO_3$, 252.1600; found, 252.1614.

*2-(tert-Butyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (**2f**).* Clear crystalline solid; yield 276 mg (44%); Mp 142−143 °C; $R_f$ = 0.60 ("wet" ether). IR (film): 2923, 1704 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.96−5.76 (m, 1H), 5.61−5.42 (d, $J$ = 10.2 Hz, 1H), 3.43−3.27 (dt, $J$ = 12.6, 4.2 Hz, 1H), 3.21−3.05 (m, 2H), 2.91−2.78 (ddd, $J$ = 12.0, 5.0, 2.4 Hz, 1H), 2.78−2.63 (br s, 1H), 2.48−2.21 (m, 2H), 1.90−1.79 (m, 2H), 1.44−1.33 (s, 9H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 176.6, 172.8, 129.3, 127.3, 59.3, 45.8, 42.9, 40.8, 33.9, 28.1, 27.7, 25.5. HRMS: $m/z$ calcd for $C_{14}H_{22}NO_3$, 252.1600; found, 252.1607.

*2-(4-Methoxyphenyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2g**).* Off-white solid; yield 746 mg (98%); Mp 183−188 °C; $R_f$ = 0.31 ("wet" ether). IR (film): 2931, 1704 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.11−6.99 (m, 2H), 6.94−6.83 (m, 2H), 6.02−5.89 (m, 1H), 5.70−5.58 (d, $J$ = 10.0 Hz, 1H), 3.83−3.72 (s, 3H), 3.61−3.49 (td, $J$ = 12.5, 4.36 Hz, 1H), 3.48−3.37 (dd, $J$ = 12.4, 5.1 Hz, 1H), 3.37−3.27 (dd, $J$ = 5.4, 2.6 Hz, 1H), 2.98−2.80 (m, 2H), 2.47−2.32 (m, 2H), 2.24−2.08 (m, 1H), 2.04−1.88 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.8, 172.4, 158.8, 134.9, 129.6, 127.4, 127.1, 114.7, 55.5, 48.6, 45.0, 41.7, 34.8, 27.3, 25.4. HRMS: $m/z$ calcd for $C_{17}H_{20}NO_4$, 302.1392; found, 302.1407.

*2-Mesityl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2h**).* White solid; yield 565 mg (72%); Mp 228−230 °C; $R_f$ = 0.37 ("wet" ether). IR (film): 2923, 1707 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.00−6.83 (d, $J$ = 12.4 Hz, 2H), 6.08−5.94 (m, 1H), 5.80−5.65 (d, $J$ = 10.0 Hz, 1H), 3.57−3.41 (td, $J$ = 7.8, 4.8 Hz, 1H), 3.34−3.24 (m, 1H), 3.24−3.15 (dd, $J$ = 13.0, 5.6 Hz, 1H), 3.09−2.98 (ddd, $J$ = 12.2, 5.0, 2.3 Hz, 1H), 2.98−2.87 (br s, 1H), 2.60−2.34 (m, 2H), 2.31−2.22 (s, 3H), 2.21−2.10 (m, 4H), 2.10−1.97 (m, 4H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.1, 172.3, 138.3, 136.5, 134.1, 133.6, 130.0, 129.7, 129.6, 127.9, 46.3, 46.1, 41.1, 35.0, 27.5, 26.2, 21.0, 17.3, 17.1. HRMS: $m/z$ calcd for $C_{19}H_{24}NO_3$, 314.1756; found, 314.1771.

*2-(2-Fluorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2i**).* White solid; yield 577 mg (76%); Mp 170−172 °C; $R_f$ = 0.53 ("wet" ether). IR (film): 2929, 1704 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.27−7.14 (m, 2H), 7.12−7.06 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.06−6.99 (m, 1H), 5.95−5.79 (m, 1H), 5.59−5.46 (d, $J$ = 10.1 Hz, 1H), 4.84−4.69 (d, $J$ = 14.9 Hz, 1H), 4.62−4.44 (d, $J$ = 14.9 Hz, 1H), 3.27−3.22 (m, 1H), 3.22−3.12 (m, 2H), 2.95−2.76 (m, 2H), 2.49−2.26 (m, 2H), 2.08−1.92 (m, 1H), 1.92−1.79 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 176.2, 171.8, 161.0 (d, $J$ = 244.9 Hz), 130.1 (d, $J$ = 3.9 Hz), 129.5, 129.4 (d, $J$ = 8.1 Hz), 127.4, 124.4 (d, $J$ = 3.5 Hz), 123.0 (d, $J$ = 14.8 Hz), 115.3 (d, $J$ = 21.6 Hz), 44.7, 44.32, 44.28, 41.5, 34.7, 27.0, 25.2. HRMS: $m/z$ calcd for $C_{17}H_{19}FNO_3$, 304.1349; found, 304.1367.

*2-Allyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**2j**).* Off-white solid; yield 426 mg (91%); Mp 128−130 °C; $R_f$ = 0.32 ("wet" ether). IR (film): 3017, 1706 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.88−5.71 (m, 1H), 5.71−5.54 (m, 1H), 5.54−5.42 (d, $J$ = 10.2 Hz, 1H), 5.12−4.93 (m, 2H), 4.03−3.89 (dd, $J$ = 15.3, 5.5 Hz, 1H), 3.89−3.75 (dd, $J$ = 15.3, 6.1 Hz, 1H), 3.23−2.98 (m, 3H), 2.83−2.73 (br s, 1H), 2.72−2.65 (m, 1H), 2.33−2.14 (m, 2H), 2.04−1.89 (m, 1H), 1.89−1.72 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 177.1, 170.7, 131.8, 129.2, 127.6, 117.2, 49.9, 44.0, 43.6, 41.7, 34.5, 27.0, 24.6. HRMS: $m/z$ calcd for $C_{13}H_{18}NO_3$, 236.1287; found, 236.1300.

*1-Oxo-3,4,4a,7,8,8a-hexahydro-1H-isochromene-8-carboxylic Acid (**2k**).* White solid; yield 398 mg (81%); Mp 164−166 °C; $R_f$ = 0.33 ("wet" ether). IR (film): 2927, 1710 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.94−5.76 (m, 1H), 5.61−5.43 (d, $J$ = 10.1 Hz, 1H), 4.38−4.27 (m, 1H), 4.27−4.11 (m, 1H), 3.54−3.36 (dd, $J$ = 6.8, 3.3 Hz, 1H), 3.06−2.91 (br s, 1H), 2.75−2.62 (ddd, $J$ = 11.0, 5.9, 3.3 Hz, 1H), 2.56−2.29 (m, 2H), 2.29−2.12 (m, 1H), 1.84−1.67 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 178.0, 171.5, 128.4, 128.0, 66.3, 41.0, 40.2, 32.7, 28.5, 23.0. HRMS: $m/z$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0817.

*2-Benzyl-8-methyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**4**).* (*E*)-*N*-Benzylhexa-3,5-dien-1-amine (**1a**) (5.0 mmol, 935 mg) was added to a round-bottomed flask, dissolved in dichloroethane (1.0 mL), and cooled to 0 °C. Citraconic anhydride (5.50 mmol, 616 mg) was then weighed and added in one portion to the diene solution. The resulting mixture was allowed to stir at 0 °C for 10 min, then heated to 60 °C and maintained there for 8 h. Upon cooling, the reaction was diluted with dichloromethane (4.0 mL) and loaded directly onto a silica gel column. Product isolation occurred by gradient elution with 0−100% hexanes/"wet" ether. White solid; yield 798 mg (53%); Mp 167−170 °C; $R_f$ = 0.51 ("wet" ether). IR (film): 2922, 1698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.18 (m, 3H), 7.18−7.04 (m, 2H), 5.86−5.67 (m, 1H), 5.58−5.39 (d, $J$ = 10.1 Hz, 1H), 4.87−4.69 (d, $J$ = 14.8 Hz, 1H), 4.41−4.22 (d, $J$ = 14.8 Hz, 1H), 3.15−2.95 (m, 3H), 2.86−2.71 (br s, 1H), 2.71−2.50 (d, $J$ = 18.6 Hz, 1H), 2.14−1.80 (m, 3H), 1.32−1.16 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 182.1, 170.0, 137.0, 128.6, 128.4, 127.8, 127.2, 126.2, 50.4, 47.3, 43.9, 42.3, 30.6, 30.1, 27.0, 23.1. HRMS: $m/z$ calcd for $C_{18}H_{22}NO_3$, 300.1600; found, 300.1607.

*2-Benzyl-1-oxo-8a-phenyl-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid (**5**).* (*E*)-*N*-Benzylhexa-3,5-dien-1-amine (**1a**) (2.50 mmol, 468 mg) was added to a round-bottomed flask, dissolved in dichloroethane (0.5 mL), and cooled to 0 °C. The phenyl maleic anhydride (2.75 mmol, 479 mg) was then weighed and added in one portion to the diene solution. The resulting mixture was allowed to stir at 0 °C for 10 min, then heated to 60 °C and maintained there for 8 h. Upon cooling, the reaction was diluted with dichloromethane (2.0 mL) and loaded directly onto a silica gel column. Product isolation occurred by gradient elution with 0−100% hexanes/"wet" ether. White


DOI: 10.1021/acs.joc.5b00804
J. Org. Chem. XXXX, XXX, XXX−XXX

solid; yield 541 mg (60%); Mp 144−146 °C; $R_f$ = 0.58 ("wet" ether). IR (film): 3026, 1723 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.11 (m, 10H), 6.07−5.82 (m, 1H), 5.72−5.56 (dd, $J$ = 10.0, 2.1 Hz, 1H), 5.02−4.83 (d, $J$ = 14.3 Hz, 1H), 4.70−4.50 (d, $J$ = 14.3 Hz, 1H), 3.56−3.42 (m, 1H), 3.26−3.16 (m, 2H), 2.97−2.80 (m, 1H), 2.75−2.47 (m, 2H), 1.86−1.67 (m, 1H), 1.63−1.46 (m, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 174.0, 173.6, 140.5, 135.6, 129.03, 128.98, 128.8, 128.3, 128.1, 127.8, 127.7, 53.9, 52.8, 51.7, 44.5, 42.9, 28.3, 22.7. HRMS: $m/z$ calcd for $C_{23}H_{24}NO_3$, 362.1756; found, 362.1773.

**General Procedure for NMR Experiments (Table 3).** The substituted aniline diene (0.35 mmol) was added to a dry 5 mm NMR tube. TMS (0.18 mmol, 0.024 mL) was added, and the sample was diluted with *d*-dichloroethane (0.20 mL). The sample was then injected into a 400 MHz Bruker NMR already stabilized at 60 °C. After allowing 15 min for temperature equilibration, the sample was locked, shimmed, and an acquisition performed. The sample was then ejected, maleic anhydride immediately added, and injected back into the NMR. The sample was then locked and shimmed. This process (addition, injection, lock, and shim) accounted for an average delay of 5 min before the time course acquisition began. A time course study was then initiated utilizing a single pulse experiment (without steady-state scans) with subsequent delay resulting in an acquisition every 2 min. Because of the nearly neat conditions, quality spectra were observed despite the single pulse. Initial qNMR sequences demonstrated relaxations within normal set parameters but were inconsequential due to the use of such long relaxation times (delay) and the absence of steady-state scans. The exotherm observed in larger scale reactions was controlled by slightly more dilution in these runs (5.0 M vs 1.8M), which also accounted for the longer reaction times. The rate of reaction was monitored by the comparative integration of at least two sets of protons in each sample. The times (min) taken for each substrate to reach 10, 25, 50, and 75% conversion are listed in Table 3.

## ■ ASSOCIATED CONTENT

### Supporting Information

Summary of computational data, additional experiments, $^{13}C$ NMR spectra of new compounds, CIF files of X-ray structures of compounds **4** and **5**, and Mol file of computed structures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00804.

## ■ AUTHOR INFORMATION


### Corresponding Author

*Fax: 785-864-5326. E-mail: jaube@ku.edu.

### Present Addresses

[§](S.S.) University of Saint Joseph, School of Pharmacy, 229 Trumbull Street, Hartford, CT 06103.

[∥](P.G.) Centre for Applied Chemistry, Central University of Jharkhand, Ranchi 835205, India.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge Kevin Frankowski and Sarah Scarry for helpful discussions, Justin Douglas for assistance with NMR, Benjamin Neuenswander for HR-MS and HPLC purity data, Prashi Jain for editorial assistance, and Laura Bohn and co-workers at the Scripps Research Institute (Jupiter, FL) for numerous collaborative efforts underscoring the value of isoquinolinones in biology, which led to the present study. We also thank Dr. Victor Day for the molecular structures of **4** and **5** based on X-ray diffraction analysis (instrument obtained through NSF-MRI grant CHE-0923449). This work was supported by the National Institute on Drug Abuse through grant DA031927 (L.B. and J.A., coprincipal investigators). We gratefully acknowledge computational support from the NSF XSEDE program.

## ■ REFERENCES


(1) (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, *2007*, 1−21. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186. (d) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (e) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157. (f) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206.

(2) (a) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992. (b) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933−1952. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

(3) Paquette, L. A.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1973**, *96*, 4671−4673.

(4) Bilovic, D. *Croat Chem. Acta* **1968**, *40*, 15−22.

(5) Frankowski, K. J.; Hirt, E. E.; Zeng, Y.; Neuenswander, B.; Fowler, D.; Schoenen, F.; Aubé, J. *J. Comb. Chem.* **2007**, *9*, 1188−1192.

(6) Frankowski, K. J.; Ghosh, P.; Setola, V.; Tran, T. B.; Roth, B. L.; Aubé, J. *ACS Med. Chem. Lett.* **2010**, *1*, 189−193.

(7) Zhou, L.; Lovell, K. M.; Frankowski, K. J.; Slauson, S. R.; Phillips, A. M.; Streicher, J. M.; Stahl, E.; Schmid, C. L.; Hodder, P.; Madoux, F.; Cameron, M. D.; Prisinzano, T. E.; Aubé, J.; Bohn, L. M. *J. Biol. Chem.* **2013**, *288*, 36703−36716.

(8) Aube, J.; Roth, B. L.; Ghosh, P.; Frankowski, K. J. Preparation of Functionalized Octahydroisoquinolin-1-one-8-carboxamides, Octahydro-isoquinolin-1-one-8-carboxylic esters, and Analogs as Opioid Receptor Modulators Useful in the Treatment of Diseases. US20100256142A1, 2010.

(9) (a) Pelter, A.; Singaram, B. *Tetrahedron Lett.* **1982**, *23*, 245−248. (b) Pelter, A.; Singaram, B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1383−1386.

(10) Imagawa, T.; Nakagawa, T.; Matsuura, K.; Akiyama, T.; Kawanisi, M. *Chem. Lett.* **1981**, *10*, 903−904.

(11) For another application, see: Brettle, R.; Cummings, D. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2385−2392.

(12) McDaniel, K. F.; Weekly, R. M. *J. Chem. Educ.* **1997**, *74*, 1465.

(13) (a) Brun, P.; Zylber, J.; Pepe, G.; Reboul, J.-P. *Heterocycl. Commun.* **1994**, *1*, 13−16. (b) Pepe, G.; Reboul, J.-P.; Brun, P.; Zylber, J. *Acta Crystallogr., Sect. C* **1995**, *C51*, 729−32. (c) Zylber, J.; Tubul, A.; Brun, P. *Tetrahedron: Asymmetry* **1995**, *6*, 377−380.

(14) (a) Varlamov, A. V.; Sidorenko, N. V.; Zubkov, F. I.; Chernyshev, A. I. *Chem. Heterocycl. Compd.* **2002**, *38*, 490−491. (b) Varlamov, A. V.; Zubkov, F. I.; Boltukhina, E. V.; Sidorenko, N. V.; Borisov, R. S. *Tetrahedron Lett.* **2003**, *44*, 3641−3643. (c) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Varlamov, A. V. *Tetrahedron* **2004**, *60*, 8455−8463. (d) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Borisov, R. S.; Varlamov, A. V. *Tetrahedron* **2005**, *61*, 4099−4113. (e) Kachkovskyi, G. O.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 12576−12582. (f) Islas-Jácome, A.; González-Zamora, E.; Gámez-Montaño, R. *Tetrahedron Lett.* **2011**, *52*, 5245−5248.

(15) Crisp, G. T.; Gebauer, M. G. *J. Org. Chem.* **1996**, *61*, 8425−8431.

(16) Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 985−995.

(17) Mellor, J. M.; Wagland, A. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 997−1005.

(18) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892−14895.

(19) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257−3262.

(20) (a) Guo, R.; Li, K.-N.; Gong, L.-Z. *Org. Biomol. Chem.* **2013**, *11*, 6707−6712. (b) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, *136*, 4492−4495.




DOI: 10.1021/acs.joc.5b00804
*J. Org. Chem.* XXXX, XXX, XXX−XXX

(21) Nair, R. V.; Baravkar, S. B.; Ingole, T. S.; Sanjayan, G. J. *Chem. Commun. (Cambridge, U. K.)* **2014**, *50*, 13874−13884.
(22) Frankowski, K. J.; Hedrick, M. P.; Gosalia, P.; Li, K.; Shi, S.; Whipple, D.; Ghosh, P.; Prisinzano, T. E.; Schoenen, F. J.; Su, Y.; Vasile, S.; Sergienko, E.; Gray, W.; Hariharan, S.; Milan, L.; Heynen-Genel, S.; Mangravita-Novo, A.; Vicchiarelli, M.; Smith, L. H.; Streicher, J. M.; Caron, M. G.; Barak, L. S.; Bohn, L. M.; Chung, T. D.; Aube, J. *ACS Chem. Neurosci.* **2012**, *3*, 221−236.
(23) (a) Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012−1015. (b) Balasubramaniyan, V.; Argade, N. P. *Tetrahedron* **1989**, *45*, 835−842. (c) Baydar, A. E.; Boyd, G. V. *J. Chem. Soc., Chem. Commun.* **1976**, 718−719.
(24) Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A., Jr.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Yeh Lin, C.; Van Voorhis, T.; Hung Chien, S.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C.-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Min Rhee, Y.; Ritchie, J.; Rosta, E.; David Sherrill, C.; Simmonett, A. C.; Subotnik, J. E.; Lee Woodcock, H., III; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer Iii, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172−3191.
(25) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490−519.
(26) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Lynch, B. J.; Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2003**, *107*, 1384−1388. (c) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian*; Gaussian, Inc.: Wallingford, CT, 2004.
(28) Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475−2532.
(29) (a) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715−4720. (b) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649−10650.
(30) Gschwend, H. W.; Lee, A. O.; Meier, H. P. *J. Org. Chem.* **1973**, *38*, 2169−2175.
(31) Yanai, H.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 7087−7093.
(32) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2000**, *66*, 1938−1940.
(33) Bally, T.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 4818−4830.
(34) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2011**, *112*, 1839−1862.
(35) (a) Samuilov, Y. D.; Uryadova, L. F.; Konovalov, A. I. *Zh. Org. Khim.* **1979**, *15*, 977−83. (b) Samuilov, Y. D.; Nurullina, R. L.; Uryadova, L. F.; Konovalov, A. I. *Zh. Org. Khim.* **1980**, *16*, 1858−63. (c) Kiselev, V. D.; Khuzyasheva, D. G.; Konovalov, A. I. *Zh. Org. Khim.* **1983**, *19*, 1268−73. (d) Nagiev, Y. M.; Samuilova, Y. D.; Bagirov, S. T.; Shnulin, A. N.; Adigezalov, V. A.; Nasibov, S. S.; Pashaev, B. K.; Shakhtakhtinskii, T. N. *Zh. Org. Khim.* **1992**, *28*, 1643−6. (e) Levkov, I. V.; Cassel, S.; Voitenko, Z. V.; Palamarchuk, G. V.; Shishkin, O. V.; Shishkina, S. V.; Lattes, A.; Rico-Lattes, I. *Heterocycles* **2012**, *85*, 1671−1681.
(36) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(37) (a) Bradley, D. *Chem. Br.* **2002**, *38*, 42−45. (b) Bougrin, K.; Loupy, A.; Soufiaoui, M. *J. Photochem. Photobiol., C* **2005**, *6*, 139−167. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140−4182. (d) Marvaniya, H. M.; Modi, K. N.; Sen, D. J. *Int. J. Drug Dev. Res.* **2011**, *3*, 34−43. (e) Varma, R. S. *Pure Appl. Chem.* **2013**, *85*, 1703−1710. (f) Banon-Caballero, A.; Guillena, G.; Najera, C. *Mini-Rev. Org. Chem.* **2014**, *11*, 118−128. (g) Olszewski, T. K. *Synthesis* **2014**, *46*, 403−429 27 pp..
(38) (a) Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Preto, P.; Moreno, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3595−8. (b) Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A.; Langa, F.; Prange, T.; Neuman, A. *J. Org. Chem.* **1995**, *60*, 4160−6. (c) Diaz-Ortiz, A.; Carrillo, J. R.; Diez-Barra, E.; de la Hoz, A.; Gomez-Escalonilla, M. J.; Moreno, A.; Langa, F. *Tetrahedron* **1996**, *52*, 9237−9248. (d) Diaz-Ortiz, A.; Carrillo, J. R.; Gomez-Escalonilla, M. J.; De la Hoz, A.; Moreno, A.; Prieto, P. *Synlett* **1998**, 1069−1070. (e) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (f) Diaz-Ortiz, A.; De la Hoz, A.; Moreno, A.; Prieto, P.; Leon, R.; Herrero, M. A. *Synlett* **2002**, 2037−2038. (g) Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M.; Carrillo, J. R.; Diaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Synlett* **2003**, 1415−1418. (h) Du, H.; Zhao, D.; Ding, K. *Chem.—Eur. J.* **2004**, *10*, 5964−5970. (i) Imachi, S.; Onaka, M. *Tetrahedron Lett.* **2004**, *45*, 4943−4946. (j) Kumamoto, K.; Fukada, I.; Kotsuki, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2015−2017. (k) Loupy, A.; Maurel, F.; Sabatie-Gogova, A. *Tetrahedron* **2004**, *60*, 1683−1691. (l) Cheng, K.; Lin, L.; Chen, S.; Feng, X. *Tetrahedron* **2005**, *61*, 9594−9599. (m) Khazaei, A.; Zolfigol, M. A.; Manesh, A. A. *J. Chin. Chem. Soc. (Taipei, Taiwan)* **2005**, *52*, 515−518. (n) Pinto, D. C. G. A.; Silva, A. M. S.; Brito, C. M.; Sandulache, A.; Carrillo, J. R.; Prieto, P.; Diaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2005**, 2973−2986. (o) Diaz-Ortiz, A.; De Cozar, A.; Prieto, P.; De la Hoz, A.; Moreno, A. *Tetrahedron Lett.* **2006**, *47*, 8761−8764. (p) Fringuelli, F.; Girotti, R.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2006**, *8*, 2487−2489. (q) Fringuelli, F.; Girotti, R.; Pizzo, F.; Zunino, E.; Vaccaro, L. *Adv. Synth. Catal.* **2006**, *348*, 297−300. (r) Masaki, Y.; Yamada, T.; Kawai, H.; Itoh, A.; Arai, Y.; Furukawa, H. *Synlett* **2006**, 288−290. (s) Nagaiah, K.; Sreenu, D.; Rao, R. S.; Vashishta, G.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 4409−4413. (t) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *Synlett* **2006**, 1369−1373. (u) Keglevich, G.; Dudas, E. *Synth. Commun.* **2007**, *37*, 3191−3199. (v) Pei, W.; Wang, Y.-J.; Yu, C.-Q. *Chin. J. Chem.* **2007**, *25*, 814−817. (w) Songis, O.; Didierjean, C.; Laurent, C.; Martinez, J.; Calmes, M. *Eur. J. Org. Chem.* **2007**, 3166−3172. (x) Shen, S.-S.; Ji, S.-J. *Chin. J. Chem.* **2008**, *26*, 935−940. (y) Ziarani, G. M.; Badiei, A.; Miralami, A. *Bull. Korean Chem. Soc.* **2008**, *29*, 47−50. (z) Hsu, C.-C.; Lai, C.-C.; Chiu, S.-H. *Tetrahedron* **2009**, *65*, 2824−2829. (aa) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Elguero, J.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2009**, 4468−4479. (ab) Victoria Gomez, M.; Aranda, A. I.; Moreno, A.; Cossio, F. P.; de Cozar, A.; Diaz-Ortiz, A.; de la Hoz, A.; Prieto, P. *Tetrahedron* **2009**, *65*, 5328−5336. (ac) Bellezza, F.; Cipiciani, A.; Costantino, U.; Fringuelli, F.; Orru, M.; Piermatti, O.; Pizzo, F. *Catal. Today* **2010**, *152*, 61−65. (ad) Flores-Larios, I. Y.; Lopez-Garrido, L.; Martinez-Martinez, F. J.; Gonzalez, J.; Garcia-Baez, E. V.; Cruz, A.; Padilla-Martinez, I. I. *Molecules* **2010**, *15*, 1513−1530. (ae) Korotaev, V. Y.; Sosnovskikh, V. Y.; Barabanov, M. A.; Yasnova, E. S.; Ezhikova, M. A.; Kodess, M. I.; Slepukhin, P. A. *Tetrahedron* **2010**, *66*, 1404−1409. (af) Nascimento-Junior, N. M.; Mendes, T. C. F.; Leal, D. M.; Correa, C. M. N.; Sudo, R. T.; Zapata-Sudo, G.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 74−77. (ag) Fort, E. H.; Scott, L. T. *Tetrahedron Lett.* **2011**, *52*, 2051−2053. (ah) Bhuyan, D.; Sarma, R.; Prajapati, D. *Tetrahedron Lett.* **2012**, *53*, 6460−6463. (ai) Flores-Conde, M. I.; Reyes, L.; Herrera, R.; Rios, H.; Vazquez, M. A.; Miranda, R.; Tamariz, J.; Delgado, F. *Int. J. Mol. Sci.* **2012**, *13*, 2590−


DOI: 10.1021/acs.joc.5b00804
*J. Org. Chem.* XXXX, XXX, XXX−XXX

2617. (aj) Palaniappan, S.; Rajender, B.; Umashankar, M. *J. Mol. Catal. A: Chem.* **2012**, *352*, 70−74. (ak) Attanasi, O. A.; Bianchi, L.; D'Auria, M.; Mantellini, F.; Racioppi, R. *Curr. Org. Synth.* **2013**, *10*, 631−639. (al) Sun, D.; Sato, F.; Yamada, Y.; Sato, S. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 276−282. (am) Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7668−7700. (an) Bhuyan, D.; Sarmah, M. M.; Dommaraju, Y.; Prajapati, D. *Tetrahedron Lett.* **2014**, *55*, 5133−5136. (ao) de los Santos, J. M.; Ignacio, R.; Es Sbai, Z.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2014**, *79*, 7607−7615. (ap) Parmar, N. J.; Labana, B. M.; Barad, H. A.; Kant, R.; Gupta, V. K. *Monatsh. Chem.* **2014**, *145*, 1179−1189. (aq) Pigott, A. J.; Lepage, R. J.; White, J. M.; Coster, M. J. *Tetrahedron Lett.* **2014**, *55*, 6864−6867.

(39) (a) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447−4450. (b) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634−2640.

(40) (a) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955−3975. (b) Terauchi, J.; Curran, D. P. *Tetrahedron: Asymmetry* **2003**, *14*, 587−592. (c) Guthrie, D. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 15492−15500.

(41) (a) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923−12931. (b) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494−495. (c) Takahashi, M.; Tanabe, H.; Nakamura, T.; Kuribara, D.; Yamazaki, T.; Kitagawa, O. *Tetrahedron* **2010**, *66*, 288−296. (d) Ayitou, A. J.-L.; Sivaguru, J. *Chem. Commun. (Cambridge, U. K.)* **2011**, *47*, 2568−2570.

(42) Nguyen, Q. N. N.; Tantillo, D. J. *Chem.—Asian J.* **2014**, *9*, 674−680.

(43) Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, *6*, 699−702.

(44) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873−879.

(45) Taber, D. F.; Pan, Y.; Zhao, X. *J. Org. Chem.* **2004**, *69*, 7234−7240.



DOI: 10.1021/acs.joc.5b00804
*J. Org. Chem.* XXXX, XXX, XXX−XXX