Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

# Synthesis of 1,2-Oxazinanes via Hydrogen Bond Mediated [3 + 3] Cycloaddition Reactions of Oxyallyl Cations with Nitrones

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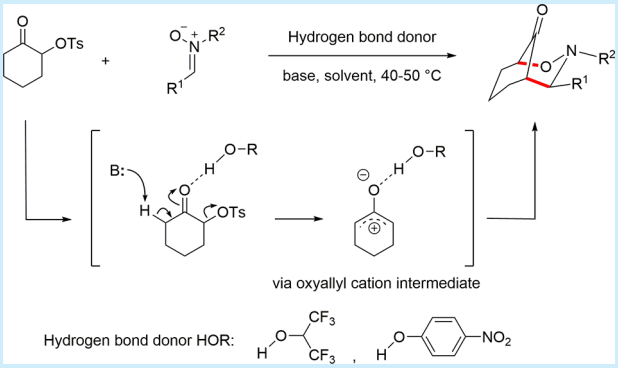
Supporting Information

**ABSTRACT:** Reported herein is the development of [3 + 3] cycloaddition reactions between oxyallyl cations and nitrones to yield 1,2-oxazinane heterocycles. Oxyallyl cation intermediates, generated *in situ* from α-tosyloxy ketones in the presence of hexafluoro-2-propanol (HFIP), a cosolvent, and a base, are found to react with a range of nitrones to afford 1,2-oxazinanes in good to high yields. The reactions are catalyzed by hydrogen-bond donors such as phenols and squaramides, and dramatically higher diastereoselectivities are observed with 4-nitrophenol.

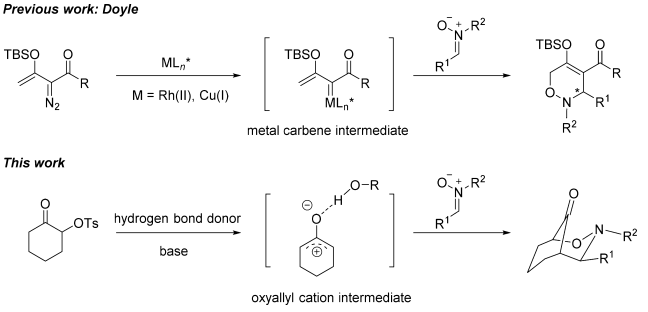





Oxyallyl cations are a powerful class of reaction intermediates with numerous applications in chemical synthesis. They can be generated by a variety of methods from readily available ketone precursors, and their unique structure and reactivity have enabled the creation of diverse C−C and C−heteroatom bond-forming processes.[1,2] In this regard, the most widely adopted reaction of oxyallyl cations is the concerted [4 + 3] cycloaddition with dienes to form the cycloheptanone scaffold, a transformation that has been incorporated in many natural product syntheses.[3] The related formal [3 + 2] cycloaddition reaction of oxyallyl cations with activated π bonds, such as those from enamines or indoles, provides a direct route to cyclopentanone derivatives.[4] Oxyallyl cations can impart umpolung capability, with the α-carbon exhibiting electrophilicity.[5] This type of reactivity has been demonstrated extensively through the "interrupted Nazarov" reaction and, more recently, through some alkylation reactions.[6,7] We sought to develop what is formally a [3 + 3] cycloaddition reaction of oxyallyls by taking advantage of the oxyallyl cation as a 3-carbon, 2π-electron unit and examining its reaction with 3-atom, 4π-electron species.[8−10] We report here the hydrogen-bond donor promoted [3 + 3] cycloaddition reaction of oxyallyl cations with nitrones to produce 1,2-oxazinanes.

The present study was motivated by our long-standing interest in the use of hydrogen-bond donors to modulate reactions, in conjunction with our recent exploration of catalytic processes involving oxyallyl cations.[11,12] Among the different methods for generating the oxyallyl species, Föhlisch's use of 2,2,2-trifluoroethanol (TFE) to induce the dehydrohalogenation of a haloketone in the presence of a base was appealing for its operational simplicity.[2d,13] Given their ease of preparation and reported reactivity, α-tosyloxy ketones were attractive as oxyallyl precursors.[14] We focused on the use of nitrones as the 4π-electron cycloaddition partner due to their stability and accessibility. Despite their widespread adoption as 1,3-dipoles in dipolar cycloaddition reactions, nitrones have found limited use in [3 + 3] cycloadditions.[15,16] The 1,2-oxazinane cycloadducts expected from the planned reaction are of interest for their biological properties and for their capacity to produce highly functionalized amino-alcohol products.[17] Among the few general methods for the synthesis of such heterocycles is Doyle's transition metal catalyzed reaction between nitrones and TBSO-substituted vinyl diazo substrates (Scheme 1).[15c,18] This powerful transformation necessitates the use of diazo precursors that are derived from β-dicarbonyl compounds. The envisioned [3 + 3] cycloaddition reaction was expected to join readily formed oxyallyl cation intermediates with nitrones under metal-free conditions.

**Scheme 1. Syntheses of 1,2-Oxazinanes via [3 + 3] Cycloadditions**




**Received:** July 22, 2018



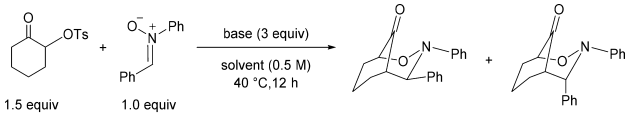

DOI: 10.1021/acs.orglett.8b02301
Org. Lett. XXXX, XXX, XXX−XXX

During the course of this work, Archambeau et al. reported closely related chemistry focusing on acyclic α-tosyloxy ketone substrates.[19]

For the initial studies, we examined the [3 + 3] cycloaddition reaction of a nitrone with α-tosyloxy ketones and $NEt_3$ in HFIP, conditions well precedented to generate oxyallyl cations. Both 2-tosyloxy-3-pentanone (**1a**) and 2-tosyloxycyclopentanone (**1b**) reacted with *N*,α-diphenyl nitrone (**2a**) to afford the desired cycloadducts at room temperature in moderate yields after 14 h (45% and 47% isolated yields, respectively), without any optimization. In contrast, 2-tosyloxycyclohexanone (**1c**) was a substantially worse reaction partner, with the cycloaddition proceeding very slowly (8% yield, by $^1$H NMR) under identical conditions. We decided to use this more challenging ketone substrate as our prototype reaction, reasoning that the optimized conditions for this substrate should also be applicable to other types of α-tosyloxy ketones.

Optimization studies for the reaction of 2-tosyloxycyclohexanone and *N*,α-diphenyl nitrone are summarized in Table 1.[20]

**Table 1. Optimization of Conditions for the Cycloaddition of 1c and 2a**




1.5 equiv (**1c**) 1.0 equiv (**2a**) (**3ca**) (**3ca'**)

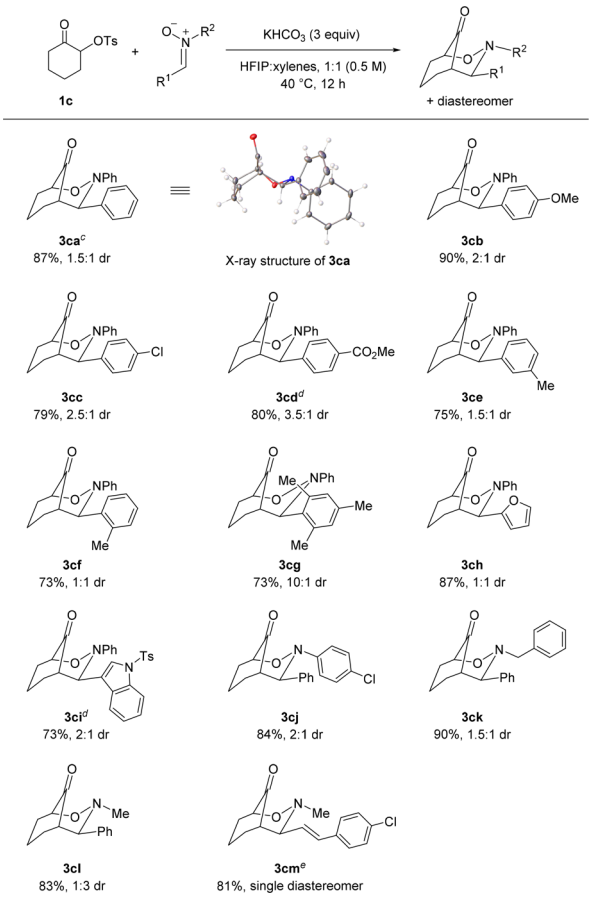
| entry | base | solvent | yield (%)[a] | dr[b] |
|---|---|---|---|---|
| 1 | $NEt_3$ | HFIP | 56 | 1:1 |
| 2 | DBU | HFIP | 16 | 1:1 |
| 3 | proton sponge | HFIP | 57 | 1.5:1 |
| 4 | 2,6-lutidine | HFIP | 62 | 1:1 |
| 5 | KOH | HFIP | 45 | 1:1 |
| 6 | $K_2CO_3$ | HFIP | 67 | 1:1 |
| 7 | $KHCO_3$ | HFIP | 77 | 1:1 |
| 8 | $KHCO_3$ | HFIP:DCE, 2:1 | 85 | 1:1 |
| 9 | $KHCO_3$ | HFIP:$CCl_4$, 2:1 | 85 | 1:1 |
| 10 | $KHCO_3$ | HFIP:xylenes, 2:1 | 86 | 1.3:1 |
| 11 | $KHCO_3$ | HFIP:xylenes, 1:1 | 90 | 1.7:1 |
| 12 | $KHCO_3$ | HFIP:xylenes, 1:2 | 85 | 2:1 |

[a]Determined by $^1$H NMR using an internal standard. [b]**3ca**/**3ca'**.

The reaction of 2-tosyloxycyclohexanone with **2a** proceeded faster at 40 °C, affording the cycloadduct in a significantly higher yield (entry 1). Raising the reaction temperature further to reflux (58 °C) had a deleterious effect on the yield (Table S1 in Supporting Information). The diastereomeric ratio of the product was not affected by temperature changes, with a 1:1 dr being observed in both cases. An extensive screening of bases revealed that weaker bases generally provided higher yields but slower conversion (Table 1, entries 1−7; Table S2). The product was formed in higher yields in the presence of heterogeneous bases than with soluble, organic bases. Of the bases screened, $KHCO_3$ gave the highest yield of the cycloadducts (entry 7).

The choice of cosolvent was likewise important. Hydrogen-bond acceptor cosolvents such as THF, ethyl acetate, and DMF led to decreased yields of the cycloadduct compared to HFIP alone (Table S3), whereas poor hydrogen bonding solvents such as 1,2-dichloroethane (DCE), carbon tetrachloride, and xylenes gave higher yields (entries 8−10, Table S4). Xylene was deemed the preferred cosolvent, as it gave a comparable yield and improved diastereoselectivity, favoring product **3ca**. The yield and diastereoselectivity of the reaction improved when the ratio of HFIP to xylenes was lowered from 2:1 to 1:1 (entry 11). Lowering the HFIP to xylene ratio further resulted in a slower reaction and a lower yield (entry 12, Table S5). The structure assigned to the major diastereomer (**3ca**) was established unambiguously through single-crystal X-ray analysis (Scheme 2).

**Scheme 2. Nitrone Scope for the [3 + 3] Cycloaddition Reaction of 2-Tosyloxycyclohexanone[a,b]**




[a]Reaction conditions: **1c** (0.75 mmol), nitrone (0.50 mmol), $KHCO_3$ (1.5 mmol), HFIP (500 μL), xylenes (500 μL), 40 °C, 12 h, isolated yields are shown. [b]Structures assigned by analogy to that of **3ca** based on $^1$H NMR. [c]Run at 1.0 mmol scale based on nitrone. [d]3 equiv of **1c** was used. [e]2 equiv of **1c** was used.

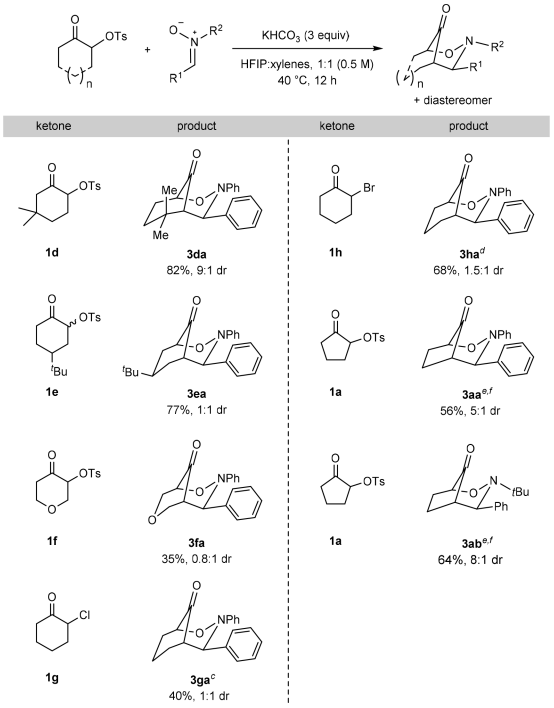
Having identified the optimal reaction conditions, we next sought to assess the scope of the cycloaddition between 2-tosyloxycyclohexanone and a variety of nitrones. Nitrones having electron-donating or electron-withdrawing groups on the α-phenyl ring of the nitrone reacted equally well, affording cycloadducts in good yields (Scheme 2, **3cb**−**3cf**). The sterically encumbered *N*-phenyl-α-mesityl nitrone reacted readily with 2-tosyloxycyclohexanone to give the expected cycloaddition product (**3cg**) in 80% yield. Despite the potential for competing [4 + 3] cycloaddition with the furan moiety,[2] *N*-phenyl,α-furyl nitrone gave only the desired [3 + 3] cycloaddition product (**3ch**). Electron-deficient *N*-*p*-chlorophenyl nitrone reacted smoothly to give product **3cj** in high


DOI: 10.1021/acs.orglett.8b02301
Org. Lett. XXXX, XXX, XXX−XXX

yield. Curiously, nitrones possessing an electron-donating substituent (methyl or methoxyl) at the *para* position of the *N*-phenyl ring gave a mixture of products, possibly due to competing Friedel–Crafts-type side reactions between the oxyallyl cation intermediate and the *N*-phenyl ring of the nitrone and/or the cycloadduct. On the other hand, *N*-alkyl nitrones such as *N*-methyl and *N*-benzyl nitrones undergo [3 + 3] cycloadditions smoothly to provide the desired products in good to high yields (**3ck**–**3cm**).

The reaction scope was explored further by examining the reaction of various α-tosyloxy-substituted cyclic and acyclic ketones (Tables 2 and 3). The *gem*-dimethyl-substituted

**Table 2. Scope of [3 + 3] Cycloaddition of Cyclic α-Tosyloxy Ketones**[a,b]

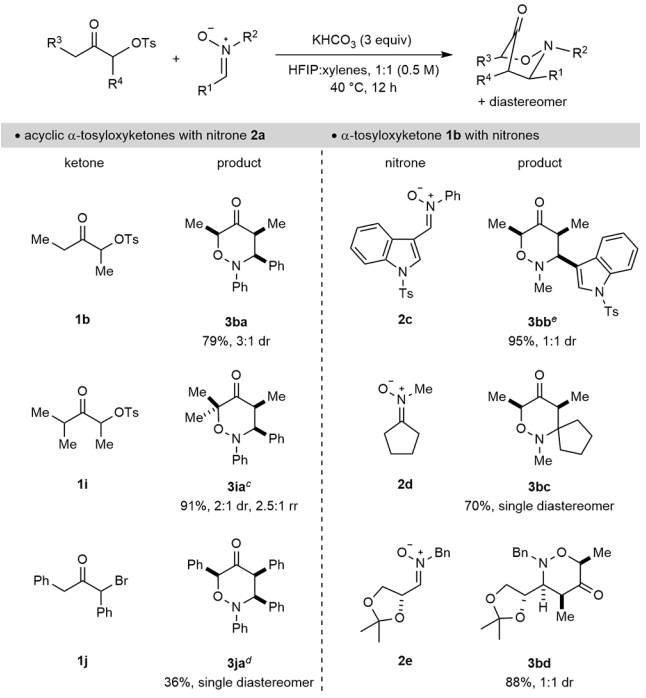



[a]Reaction conditions: ketone (0.75 mmol), **2a** (0.50 mmol), $KHCO_3$ (1.5 mmol), HFIP (500 μL), xylenes (500 μL), 40 °C, 12 h, isolated yields are shown. [b]Structures assigned by analogy to that of **3ca** based on $^1$H NMR. [c]96 h. [d]60 h. [e]Reaction run at room temperature. [f]Yield of the major diastereomer.

substrate **1d** reacted well, giving the expected cycloadduct in good yield, with unexpectedly high diastereoselectivity and complete regioselectivity. α-Chloro and α-bromo ketones (**1g** and **1h**) are also suitable reaction partners. 2-Tosyloxycyclopentanone was found to react well with nitrones. Acyclic α-tosyloxy and α-bromo ketones were also found to be effective substrates for the cycloaddition reaction (Table 3, **3ba**–**3bd**). The sterically hindered tosyloxyketone **1i** was slower to react and required the use of a stronger base ($NEt_3$), but it gave the cycloadducts (**3ia**), a mixture of diastereomers and regioisomers, in high yield.

During the cosolvent screen, we observed that with a longer reaction time the cycloaddition products were obtained in moderate yields when as little as 2 equiv of HFIP were used (Table 4, entry 1), while no product was observed in the absence of HFIP (entry 2). Reasoning that hydrogen bonding by HFIP may be facilitating the elimination of the tosyloxy

**Table 3. Scope of [3 + 3] Cycloaddition of Acyclic α-Tosyloxy Ketones**[a,b]




[a]Reaction conditions: ketone (0.75 mmol), nitrone (0.50 mmol), $KHCO_3$ (1.5 mmol), HFIP (500 μL), xylenes (500 μL), 40 °C, 12 h, isolated yields are shown. [b]Structures assigned by analogy to that of **3ca** based on $^1$H NMR. [c]$NEt_3$ (1.8 equiv), 60 h. [d]Reaction run at room temperature. [e]2 equiv of **1b** was used.

group as well as the ensuing cycloaddition, we investigated the possibility of using other hydrogen-bond donors to promote the [3 + 3] cycloaddition reaction.[21] Indeed, when HFIP was replaced with 1 equiv of various phenols, the reaction proceeded to deliver the desired products, often in good yields (entries 3–6). Lower phenol p$K_a$ was found to correlate with increased activity, and 4-nitrophenol was found to give the desired products with comparable yields as the HFIP/xylenes condition. Substoichiometric quantities of 4-nitrophenol were sufficient to catalyze the desired cycloaddition and provided better diastereoselectivities (entries 7 and 8). Alkylation of 4-nitrophenol by the oxyallyl cation intermediate was only a minor byproduct.[7b]

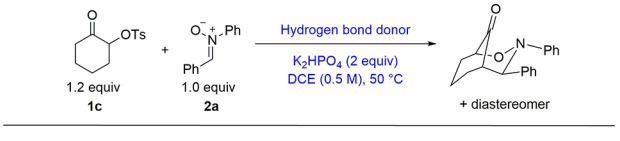
We also briefly examined the catalysis of the cycloaddition by squaramides, which have found widespread success as hydrogen-bond donor catalysts in our laboratory[22] and those of many others.[23] We were pleased to find that just 10 mol % of squaramide **4e** was sufficient to catalyze the cycloaddition reaction, giving the product in 58% yield (Table 4, entry 9). To the best of our knowledge, this result represents the first example of using a substoichiometric amount of a hydrogen-bond donor for the generation and reaction of a cyclohexanone-derived oxyallyl cation. Disappointingly, despite its higher acidity and solubility compared to **4e**, the corresponding dithiosquaramides **4f** did not catalyze the reaction.[24] Finally, we also examined catalysis of the reaction by prolinol **4g**[21] but found it to be ineffective (entry 11).

Given the significant diastereoselectivity enhancement observed when using 4-nitrophenol as a catalyst, we examined its effect on several cycloaddition substrates presented in Scheme 2. To our delight, 4-nitrophenol-catalyzed reactions

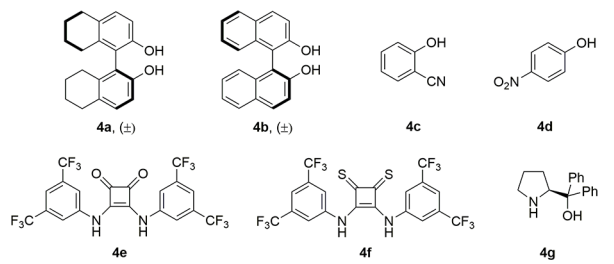


DOI: 10.1021/acs.orglett.8b02301
Org. Lett. XXXX, XXX, XXX–XXX

**Table 4. [3 + 3] Cycloaddition Promoted by Hydrogen-Bond Donor (HBD) Molecules**




Hydrogen bond donor




| entry | HBD | equivalents of HBD | time (h) | yield (%)[a] | dr[b] |
|---|---|---|---|---|---|
| 1 | HFIP | 2 | 36 | 74 | 5:1 |
| 2 | none | 0 | 36 | <2 | – |
| 3 | **4a** | 1 | 36 | 14 | 2:1 |
| 4 | **4b** | 1 | 36 | 43 | 5:1 |
| 5 | **4c** | 1 | 24 | 72 | 8:1 |
| 6 | **4d** | 1 | 18 | 84 | 7:1 |
| 7 | **4d** | 0.5 | 36 | 80 | 15:1 |
| 8 | **4d** | 0.2 | 72 | 59 | 10:1 |
| 9 | **4e** | 0.1[c] | 36 | 58 | 4:1 |
| 10 | **4f** | 0.1 | 36 | <2 | – |
| 11 | **4g** | 1 | 36 | <2 | – |

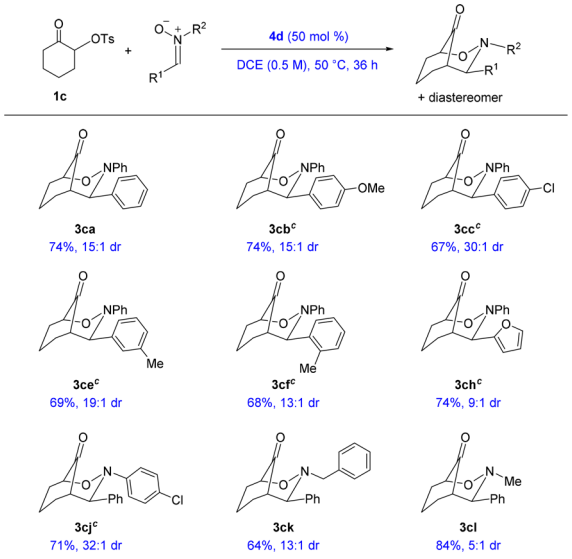
[a]Determined by $^1$H NMR using an internal standard. [b]**3ca**/**3ca′**. [c]**4e** is not fully soluble under these conditions.

afforded the cycloadducts in comparable yields to the HFIP/xylene conditions, but with considerably higher diastereomeric ratios (Scheme 3). For instance, whereas the original conditions gave products **3cc**/**3cc′** as a 2.5:1 mixture, under 4-nitrophenol catalysis conditions the ratio was 30:1. In the case of **3cl**/**3cl′**, interestingly, the two reaction conditions gave opposite diastereoselectivities.

The 1,2-oxazinanes obtained through [3 + 3] cycloadditions can be further transformed into various hydroxyl- and amine-functionalized compounds (Scheme 4). For example, reduction of **3ca** with $NaBH_4$ furnished alcohol **5** as a single diastereomer, while reductive amination provided the corresponding amine **7**, also as a single diastereomer. Subsequent cleavage of the labile N−O bond provided ring-opening products **6** and **8** in good yields.

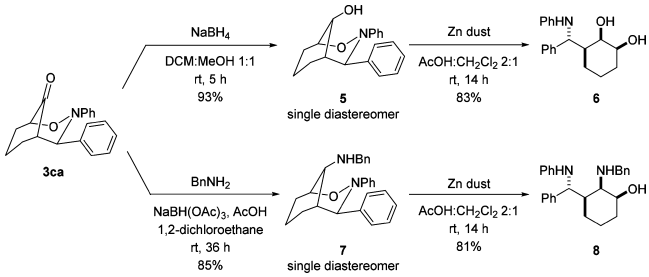
In summary, we have developed a metal-free, [3 + 3] cycloaddition reaction between nitrones and oxyallyl cations. The latter are generated in situ from readily available tosyloxy ketone precursors. The reaction enables the facile synthesis of an assortment of 1,2-oxazinanes, a heterocyclic motif that is not easily accessed through other methods. Significantly, we have discovered that hydrogen-bond donor molecules not only promote the cycloaddition reaction but also enhance its diastereoselectivity dramatically. The use of chiral hydrogen-bond donors or Brønsted acids to render these reactions enantioselective is under investigation, and the results will be reported in due course.

**Scheme 3. [3 + 3] Cycloaddition of Selected Substrates from Scheme 2 Promoted by 4-Nitrophenol as a Hydrogen-Bond Donor Catalyst[a,b]**




[a]Reaction conditions: **1c** (0.60 mmol), nitrone (0.50 mmol), $K_2HPO_4$ (1.0 mmol), **4d** (0.25 mmol), DCE (1 mL), 50 °C, 36 h, isolated yields are shown. [b]Structures assigned by analogy to that of **3ca** based on $^1$H NMR. [c]An additional 50 mol % of **4d** was added after 24 h to shorten the reaction time.

**Scheme 4. Derivatization of [3 + 3] Cycloaddition Product 3ca**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02301.

Supplemental tables and figures, experimental procedures, spectroscopic data for all new compounds, and X-ray crystallography data (PDF)

### Accession Codes

CCDC 1855847 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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DOI: 10.1021/acs.orglett.8b02301
Org. Lett. XXXX, XXX, XXX−XXX

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Science Foundation (NSF-1566402) for financial support of this work.

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DOI: 10.1021/acs.orglett.8b02301
*Org. Lett.* XXXX, XXX, XXX−XXX