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The Scope and Limitations of Intramolecular Nicholas and Pauson-Khand Reactions for the Synthesis of Tricyclic Oxygen- and Nitrogen-Containing Heterocycles

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We studied the scope and limitations of a tandem intramolecular Nicholas/Pauson-Khand strategy for the synthesis of tricyclic oxygen- and nitrogen-containing heterocycles. This methodology enables conversion of simple acyclic starting materials into a series of previously unknown heterocyclic architectures. For the preparation of cyclic ethers (Z = O), tricyclic [5,6,5]- through [5,9,5]-systems (m
= 1, n = 1-4) are available with the [5,7,5]- and [5,8,5]-systems amenable to quick and efficient synthesis. Tricyclic [5,7,5]- and [5,8,5]-amine-containing (Z = NH) heterocycles can be successfully prepared. Attempts to make larger-ring systems (Z = O, m = 2; Z = O, n = 5; or Z = NH, n = 4-5) or prepare lactones via Nicholas reactions with carboxylic acid nucleophiles (available via oxidation of alcohol nucleophiles, Z = O) result in decomposition or dimerization. The latter process enables formation of 14-, 16-, and 18-membered ring diolides when using carboxylic acid nucleophiles. We also investigated the use of chiral amine promoters in the Pauson-Khand step but found no asymmetric induction.

Introduction

Methods that enable the quick and efficient conversion of simple acyclic molecules into complex polycyclic structures are highly prized in organic chemistry. One such strategy is the combination of an intramolecular Nicholas reaction followed by an intramolecular Pauson-Khand reaction. Surprisingly, this reaction sequence was not well known at the outset of our investigation. The lone application of this strategy is in Schreiber and Jamison’s synthesis of epoxydictymene in which an intramolecular endocyclic Nicholas reaction with an allylsilane nucleophile is followed by an intramolecular Pauson-Khand reaction to provide the carbon skeleton of the target natural product. Beyond this example, nothing was known about the scope of this reaction sequence with respect to the nature of the nucleophile in the Nicholas reaction, the size of the ring generated in the Nicholas reaction, and the size of the rings generated in the Pauson-Khand reaction. Thus, we set out to systematically address all of these issues.

The overall goal of our investigation is depicted in Scheme 1. We planned to quickly generate simple, acyclic enynes 1 that, upon reaction with dicobalt octacarbonyl, would yield cobalt-alkyne complexes 2. Subsequent intramolecular Nicholas reactions would provide heterocycles 3 and, ultimately, target tricycles 4 after the Pauson-Khand reaction. Our specific goals were the following: 1) investigate alcohols (Z = O), amines (Z = NH), and carboxylic acids (available via oxidation of alcohol
nucleophiles, Z = O) as nucleophiles in intramolecular Nicholas reactions; 2) determine what sized rings (n = 1-5) could be prepared in endocyclic intramolecular Nicholas reactions; 3) study the synthesis of differently sized rings (m = 1,2) in the Pauson-Khand reaction. During the course of our investigations, we successfully achieved all of these goals.

**Scheme 1.** Overall Goal: Tandem Nicholas/Pauson-Khand Reactions for the Synthesis of Tricyclic Heterocycles

The Nicholas reaction is a highly useful inter- or intramolecular propargylic substitution reaction. Intermolecular reactions with a variety of nucleophiles are well studied, and the most common intramolecular variations involve exocyclic cyclizations with carbon nucleophiles. Intramolecular Nicholas reactions are classified as exocyclic when the cobalt-complexed alkyne ends up outside of the newly generated ring, while endocyclic cyclizations include the cobalt-alkyne complex in the newly formed ring. Of the three types of Nicholas reactions (intermolecular, exocyclic intramolecular, and endocyclic intramolecular), the endocyclic intramolecular variety is the least studied. Furthermore, use of heteroatom nucleophiles in these transformations is even less common. When thinking about intramolecular Nicholas reactions, it is important to note that the alkyne geometry is significantly altered upon complexation with cobalt. The standard 180° bond angle is reduced to 138° in these
organometallic clusters. In fact, several groups have taken advantage of this change in geometry to promote intramolecular cycloaddition reactions that were initially unfavorable due to the linear alkyne geometry. Thanks to Isobe’s pioneering investigations into the total synthesis of ciguatoxin, there are several examples of the use of alcohol nucleophiles in endocyclic intramolecular Nicholas reactions. On the other hand, endocyclic cyclizations with amine nucleophiles are unknown, and only one report of an intermolecular Nicholas reaction with a carboxylic acid existed at the outset of our research.

Intramolecular Pauson-Khand reactions for the synthesis of bicyclic carbocycles are well known. We anticipated little difficulty preparing bicyclic [5,5]-, [5,6]-, and [5,7]-systems based on the wealth of literature precedent for their construction.

**Results and Discussion**

Our initial synthetic efforts focused on the preparation of [5,6,5]- through [5,10,5]-tricyclic ethers. Thus, keeping m = 1 and Z = O (Scheme 1), we planned to vary n from 1 to 5. This would enable investigation of endocyclic intramolecular Nicholas reactions for the synthesis of 6- through 10-membered ethers followed by Pauson-Khand reactions to form the final two five-membered rings in our tricyclic targets. The enynes needed for the preparation of the 6- through 8-membered ring cyclic ethers are available in four synthetic steps starting with 4-pentenal and the appropriately sized terminal alkyne alcohol with the key transformation being an acetylide addition to 4-pentenal.

Preparation of the tricyclic [5,6,5]-system identified the limitations of our method for the synthesis of small rings via the Nicholas reaction. Beginning with 3-butyn-1-ol and 4-pentenal, enyne is available in four steps and 43% overall yield. Cobalt complexation proceeds smoothly to afford cobalt-alkyne complex. Not surprisingly, the subsequent Nicholas and Pauson-Khand reactions are highly inefficient. The strain inherent in rings of six or fewer members containing a cobalt-complexed alkyne, like 7, (ideal C-C bond angles = 138°) makes them exceedingly difficult to prepare, and we observed mainly decomposition of the cobalt-complexed starting material during the course of this reaction. The tetrasubstituted alkene generated in the Pauson-Khand reaction (7 → 8 + 9) is also strained, thus
explaining the disappointing yield for this transformation. This series of reactions clearly demonstrates that [5,6,5]-tricyclic systems are not amenable to efficient production via an intramolecular Nicholas/Pauson-Khand strategy.

Scheme 2. Synthesis of [5,6,5]-Tricyclic Ethers

Based on literature precedent from Isobe’s lab,\textsuperscript{8,15} we were optimistic that larger rings could more easily accommodate the geometrical demands of cobalt-alkyne complexes. Synthesis of the [5,7,5]-tricyclic ethers 13 and 14 provided strong support for this hypothesis. Enyne 10 can be synthesized in four steps (28\% overall) from 4-pentyn-1-ol and 4-pentenal.\textsuperscript{4a} Cobalt complexation to yield 11 is followed by a high-yielding Nicholas reaction to furnish 7-membered ring cyclic ether 12. We investigated several promoters in the Pauson-Khand step with NMO\textsuperscript{16} providing 13 and 14 in 30\% yield (72:28) and cyclohexylamine\textsuperscript{17} generating 13 and 14 in 91\% yield (42:58).\textsuperscript{18,19}
Scheme 3. Synthesis of [5,7,5]-Tricyclic Ethers

The [5,8,5]-tricyclic ethers 18 and 19 can also be prepared quickly and efficiently. Enyne 15, available in four steps and 54% overall yield from 5-hexyn-1-ol and 4-pentenal,4a reacts with dicobalt octacarbonyl to afford cobalt-complexed alkyne 16 in 98% yield. The boron trifluoride mediated Nicholas reaction provides eight-membered ring cyclic ether 17 in excellent yield, and the Pauson-Khand reaction furnishes tricycles 18 and 19 in yields ranging from 25-86% and selectivities of 55:45-89:11 depending on the specific reaction conditions.18,19
Scheme 4. Synthesis of [5,8,5]-Tricyclic Ethers

Synthesis of the [5,9,5]-tricyclic ether required the preparation of enyne 24 according to the synthetic sequence outlined in Scheme 5. Unlike the syntheses described in Schemes 2-4, the terminal alkyne starting material, 6-heptyn-1-ol (21), is prohibitively expensive. Using Denmark’s procedure,²⁰ it can be prepared by treatment of internal alkyne 20 with sodium hydride and ethylenediamine (EDA). Then, following the analogous procedure used for the synthesis of enynes 5, 10, and 15, enyne 24 can be generated in four more steps. Protection of the primary alcohol as the THP ether yields 22²¹ which is deprotonated to provide the acetylide anion that combines with 4-pentenal to furnish alcohol 23. Methylation of the secondary alcohol with sodium hydride and methyl iodide followed by removal of the THP protecting group with PPTS yields the target enyne 24.
Scheme 5. Synthesis of Enyne 24

As in previous cases, cobalt complexation of 24 to yield 25 proceeded smoothly. The subsequent Nicholas reaction to form nine-membered ring ether 26 provided the desired compound, but only in 35-52% yield. Conversion of this molecule into the tricyclic targets 27 and 28 via the Pauson-Khand reaction also proved disappointing. The reaction proceeded in only 19-27% yield; however, it was highly selective for the trans isomer.\(^1\) Of the three different conditions investigated for the Pauson-Khand reaction, cyclohexylamine\(^1\) failed to provide any product, heating the reaction in acetonitrile open to the air\(^3\) afforded 27 and 28 in a ratio of 91:9 and 19% yield, and NMO\(^1\) furnished 27% yield of 27 only. These results clearly demonstrate that, especially for the Pauson-Khand reaction, the scope for our Nicholas/Pauson-Khand strategy does not extend to a practical synthesis of [5,9,5]-tricyclic ethers.
Scheme 6. Synthesis of [5,9,5]-Tricyclic Ethers

Curious to see if the trend continued for the formation of the 10-membered ring ether, we prepared enyne 30 via the same strategy used for the preparation of the one carbon shorter enyne 24. As outlined in Scheme 7, internal alkyne 29 can be easily converted into target 30 in five synthetic steps.

Scheme 7. Synthesis of Enyne 30

Cobalt-alkyne complex 31 is available in quantitative yield from enyne 30. Unexpectedly, the subsequent Nicholas reaction provided dimeric 20-membered ring bis-ether 32 instead of the desired 10-membered ring cyclic ether. Since all of our Nicholas reactions are under thermodynamic control, this result indicates that the bis-ether is more stable than the corresponding cyclic ether. The propensity of the Nicholas reaction to favor dimerization was also demonstrated during our investigation of carboxylic
acid nucleophiles (vide infra). Although highly inefficient, we were able to isolate the pentacyclic Pauson-Khand reaction product 33 after heating open to the air in acetonitrile.³

**Scheme 8.** Synthesis of 20-Membered Ring Containing Pentacyclic Dimers

The results of our investigations into the synthesis of [5,n,5]-tricyclic ethers clearly demonstrates that the [5,7,5]- and [5,8,5]-systems are readily available. It is possible to prepare the [5,6,5]- and [5,9,5]-tricycles, although in poor overall yield. None of the target tricyclic [5,10,5]-ether can be isolated using our method; instead the dimeric 20-membered ring compound is produced.

We next studied the affect of enlarging one of the rings in the bicyclic system generated during the Pauson-Khand reaction. Specifically, we set our sights on the synthesis of a tricyclic [5,8,6]-system. A slight modification of our standard synthetic sequence, substitution of 5-hexenal for 4-pentenal enabled production of the starting enyne 34.⁴a Synthesis of cobalt-alkyne complex 35 proceeded without incident; however, the key Nicholas reaction for the production of 36 failed. Various changes to the reaction conditions never enabled isolation of cyclic cobalt alkyne complex 36. By TLC, trace amounts of target 36 appeared to be produced, but we were never able to successfully characterize this or any
other product of the reaction. We believe the failure of this reaction results from the distance between the alkene and the carbocation generated upon exposure of 35 to boron trifluoride. The alkene in the molecule is well positioned to attack the carbocation via a 5-exo or 6-endo process, thus generating a second carbocation that can participate in further polymerization or decomposition pathways. Although it may be possible to trap this carbocation with an external nucleophile, we have yet to attempt these experiments. As a consequence of our inability to synthesize 36, our subsequent investigations focused exclusively on modifications in the nature of the Nicholas reaction (structure of the nucleophile and size of the ring formed) while keeping the Pauson-Khand reaction portion of the process constant (only make [5,n,5]-tricyclic systems).

**Scheme 9.** Attempted Synthesis of [5,8,6]-Tricyclic Ethers

Interesting trends emerged when we focused on diastereoselectivities in the Pauson-Khand reactions for the synthesis of the cyclic ethers. As highlighted in Table 1, the diastereomeric ratios for the *trans* and *cis* isomers vary significantly for each substrate studied and reagents used. For the [5,7,5]-tricyclic ethers, two of the reagents yield the *cis* isomer as the major product, while the other two favor the *trans*. But for the [5,8,5]-system, all conditions favor production of the *trans* diastereomer. Cyclohexylamine
and acetonitrile in air both follow the same trends, favoring the cis isomer in the [5,7,5]-system and the trans isomer in the [5,8,5] case. *N*-Methylmorpholine-*N*-oxide (NMO)\(^{16}\) and isopropyl methyl sulfide\(^{22}\) also appear similar, providing nearly identical ratios in both the [5,7,5]- and [5,8,5]-systems and always favoring formation of the trans isomer.

**Table 1.** Selectivity in the Pauson-Khand Reaction for the Synthesis of Tricyclic Ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>([5,6,5]-Products)</th>
<th>([5,7,5]-Products)</th>
<th>([5,8,5]-Products)</th>
<th>([5,9,5]-Products)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 (<em>{trans}) 9 (</em>{cis})</td>
<td>13 (<em>{trans}) 14 (</em>{cis})</td>
<td>18 (<em>{trans}) 19 (</em>{cis})</td>
<td>27 (<em>{trans}) 28 (</em>{cis})</td>
</tr>
<tr>
<td>1</td>
<td>CyNH(_2),  (\Delta)</td>
<td>-</td>
<td>42 58</td>
<td>74 26</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)CN,  air,  (\Delta)</td>
<td>66 34</td>
<td>37 63</td>
<td>55 45</td>
<td>91 9</td>
</tr>
<tr>
<td>3</td>
<td>NMO</td>
<td>-</td>
<td>72 28</td>
<td>88 12</td>
<td>100 0</td>
</tr>
<tr>
<td>4</td>
<td>(i)-PrSMe, (\Delta)</td>
<td>-</td>
<td>67 33</td>
<td>86 14</td>
<td>-</td>
</tr>
</tbody>
</table>

We do not have a satisfactory explanation for the diastereoselectivity differences in the Pauson-Khand reactions of our cyclic ethers. In Scheme 10, we outline the stereochemical determining steps in the mechanism of the formation of the [5,8,5] cyclic ethers 18 and 19. Alkene association of the free alkene to one of the cobalt atoms in 17 can yield either complex A or complex C. (Note: The CO ligands in intermediates A-D have been omitted for clarity.) Complex A, with the ether oxygen in a pseudo-equatorial orientation, undergoes alkene insertion to ultimately produce the trans product isomer 18. On the other hand, complex C, with the ether oxygen in a pseudo-axial orientation, undergoes alkene insertion to ultimately produce the cis product isomer 19. The different Pauson-Khand promoters must influence key alkene insertion steps (A→B and C→D); however, it is not clear to us how to accurately explain the results in Table 1.
We next turned to our goal of using this strategy for the synthesis of tricyclic amines. Synthesis of the Nicholas reaction precursor 39 proved straightforward since we were able to modify the sequence previously employed for the synthesis of the [5,7,5]-tricyclic ethers by inserting a Mitsunobu reaction\textsuperscript{23} prior to the cobalt complexation step. Enyne 10 is converted into tosylamine 39 in high yield via a Mitsunobu reaction\textsuperscript{24} and exposure to dicobalt octacarbonyl. A Nicholas reaction with either boron trifluoride or tetrafluoroboric acid provides cyclic amine 40 in greater than 70% yield. The subsequent Pauson-Khand reaction furnishes exclusively the \textit{cis} diastereomer 42 in excellent yield regardless of the conditions employed (cyclohexylamine, NMO, or acetonitrile and air).
We were thrilled by the results of both the Nicholas and Pauson-Khand steps in this sequence. This is the first example of a successful endocyclic intramolecular Nicholas reaction using an amine nucleophile, and the Pauson-Khand reaction proved highly efficient and completely selective for only one isomer.

The exclusive formation of 42 stimulated us to consider options for an asymmetric Pauson-Khand reaction using this system. Milet and Gimbert recently published a computational study focused on the role of Lewis base promoters in the Pauson-Khand reaction in which they conclude that the Lewis base renders the olefin insertion step in the mechanism irreversible.\textsuperscript{25} In their mechanistic analysis, the amine is bound to cobalt during the entire mechanism, and, presumably, could play a crucial role in determining the stereochemical outcome of the reaction. Thus, the question we aimed to address was, could the use of chiral amine promoters generate asymmetry in the Pauson-Khand reaction? Kerr and Laschat had independently shown that chiral $N$-oxides, namely brucine $N$-oxide and sparteine $N$-oxide, respectively, could induce asymmetry in Pauson-Khand reactions solely from the asymmetric nature of the promoter.\textsuperscript{26}
Since only one diastereomer is produced in the Pauson-Khand reaction of 40, this was the ideal substrate to investigate. However, reactions with a variety of commercially available chiral primary amines did not lead to any detectable asymmetric induction as measured by chiral GC. The amines pictured in Figure 1 led to formation of 42 in varying yields but always as a racemic mixture. Thus, we concluded that this idea holds no promise for our system, but we hope that others will investigate this strategy for the asymmetric Pauson-Khand reaction. This approach could provide a simple and cost-effective option for the asymmetric synthesis of chiral cyclopentenones.

**Figure 1.** Chiral Amines Investigated as Promoters of Asymmetric Pauson-Khand Reactions

Continuing our investigation into the synthesis of tricyclic amines, we converted enyne 15 into cobalt-alkyne complex 43 after the requisite Mitsunobu reaction and cobalt complexation steps. The subsequent Nicholas reaction was successful; however, it only proceeded in 20-41% yield. The target tricycles 45 and 46 are available in 41-69% yield using our standard Pauson-Khand reaction conditions. The selectivity for each reaction is shown in Table 2.
Scheme 12. Synthesis of [5,8,5]-Tricyclic Amines

Table 2. Selectivity in the Pauson-Khand Reaction for the Synthesis of [5,8,5]-Tricyclic Amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(44 → 45 + 46)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CyNH₂, Δ</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN, Δ</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>NMO</td>
<td>41</td>
</tr>
</tbody>
</table>

The reactions of cyclic amines 40 and 44 demonstrate the preference of these substrates to form cis diastereomers 42 and 46, respectively. In Scheme 13, the key intermediates resulting from alkene association and alkene insertion in the Pauson-Khand mechanism for the reaction of 44 are illustrated. The additional steric demands imposed by the tosyl group in intermediates E-H versus the corresponding oxygen-containing intermediates A-D destabilize the pathway leading to the trans cyclic amine product 45. Especially in the seven-membered ring cyclic amine reaction (40→42, Scheme 11), intermediates similar to G and H are favored and lead to exclusive production of the cis tricyclic product 42.
Scheme 13. Origin of Diastereoselectivity in the Pauson-Khand Reaction of Amine 44

Schemes 14 and 15 illustrate our unsuccessful attempts to prepare [5,9,5]- and [5,10,5]-tricyclic amines (49 + 50 and 53 + 54), respectively. In both of these cases, the requisite Nicholas reaction precursors (47 and 51) were prepared without incident. However, we could never obtain the Nicholas reaction products 48 or 52 upon exposure of the precursors to either boron trifluoride or tetrafluoroboric acid. The cobalt complexed alkynes 47 and 51 were simply unreactive under our Nicholas reaction conditions. We observed traces of the desired products by TLC but were never able to isolate enough material to adequately characterize them. We concluded that, unlike the 7- and 8-membered ring cyclic amines 40 and 44, respectively, 48 and 52 are not thermodynamically favored in these reactions.
Scheme 14. Attempted Synthesis of [5,9,5]-Tricyclic Amines

Scheme 15. Attempted Synthesis of [5,10,5]-Tricyclic Amines
Since we were unable to obtain the 9- and 10-membered ring cyclic amines, the scope of the intramolecular Nicholas/Pauson-Khand strategy for the synthesis of cyclic amines is limited to the production of the [5,7,5]- and [5,8,5]-systems. Most importantly, the tricycle containing the seven-membered ring is available via a highly selective and efficient sequence. Thus, we have demonstrated that intramolecular endocyclic Nicholas reactions with amine nucleophiles work well for the synthesis of 7- and 8-membered rings.

Our next objective was investigation of the behavior of carboxylic acid nucleophiles in intramolecular Nicholas reactions in hopes of preparing a variety of lactones. Due to the limitations already described, we confined our experiments to the preparation of [5,7,5]-, [5,8,5]-, and [5,9,5]-tricyclic lactones.

We could easily access the substrates required for the Nicholas/Pauson-Khand investigation by simply oxidizing the starting materials used in the cyclic ether syntheses. For example, a two-step oxidation sequence involving the Dess-Martin periodinane\textsuperscript{27} followed by treatment with Oxone\textsuperscript{28} converts alcohol 10 into the corresponding carboxylic acid in good yield. Subsequent cobalt complexation provided the Nicholas reaction precursor 55 in 85% yield.\textsuperscript{29} The Nicholas reaction itself proved disappointing, yielding none of the desired lactone and only 18% of dimeric 14-membered ring diolide 56\textsuperscript{30} which did not participate in the Pauson-Khand reaction to provide 57.
Substrates for the synthesis of the 8- and 9-membered ring lactones also dimerize to the 16- and 18-membered ring diolides, respectively. As in the synthesis of the 14-membered ring diolide, the oxidation and cobalt complexation reactions proceed smoothly to provide high yields of the cobalt-alkyne complexes 58 and 61. Upon exposure to tetrafluoroboric acid, 58 affords the 16-membered ring diolide 59 in good yield, while 61 provides 18-membered ring 62 in only 9% yield. In the reactions to form the 14-membered ring diolide 56 and the 18-membered ring diolide 62, we attribute the poor yields to a significant amount of unreacted starting material and formation of uncharacterizable byproducts. Our Nicholas reactions with carboxylic acid nucleophiles are under thermodynamic control, and these results indicate that starting materials 55 and 61 are more stable than the corresponding diolide products. Only 16-membered ring diolide 59 shows enhanced stability versus its Nicholas reaction precursor, carboxylic acid 58.
Scheme 17. Synthesis of 16-Membered Ring Diolides

1) Dess-Martin, 90-97%
2) Oxone, 94-96%
3) Co$_2$(CO)$_8$, 86-97%

Scheme 18. Synthesis of 18-Membered Ring Diolides

1) Dess-Martin, 83%
2) Oxone, 100%
3) Co$_2$(CO)$_8$, 52%
As seen with diolide 56, neither 59 nor 62 participate in the Pauson-Khand reaction. We have no satisfying explanation for these surprising results. Experimentally, these reactions suffer from poor mass recovery indicating decomposition of starting material, and we have no evidence of even trace production of the desired Pauson-Khand targets. These results appear related to the Pauson-Khand reaction of 20-membered ring bis-ether 32 (Scheme 8) that proceeds in only 11% yield. It is possible that structural constraints inherent in diolides 56, 59, and 62 do not allow proper alignment for the formation of the bicyclo[5,5] systems, whereas larger bicyclic systems (bicyclo[5,6] and bicyclo[5,7]) might form more easily.

Our investigations into the syntheses of lactones via intramolecular Nicholas reactions were unsuccessful. We observed none of the desired lactone targets in any of the three cases studied and only obtained reasonable yields for the 16-membered ring diolide. Nonetheless, the first step in the formation of our three diolides marks only the second report of an intermolecular Nicholas reaction with a carboxylic acid nucleophile, while the second step in the diolide formation constitutes the first example of an intramolecular Nicholas reaction with a carboxylic acid nucleophile. Given the known difficulties in the formation of medium sized lactone rings, it is not surprising that our method yields only diolide products. As stated previously, our Nicholas reactions are thermodynamically controlled, and the large sized diolides are clearly more stable than the target lactones.

Conclusions

In summary, we have demonstrated the scope and limitations of a tandem intramolecular Nicholas/Pauson-Khand strategy for the synthesis of tricyclic oxygen- and nitrogen-containing heterocycles. We can successfully prepare a variety of [5,n,5]-tricyclic systems; however, difficulties in the Nicholas reaction with an appropriately functionalized substrate prevented the synthesis of [5,n,6]-systems. Intramolecular Nicholas reactions with alcohol nucleophiles have broader scope than the corresponding amine or carboxylic acid nucleophiles. Our best cases were syntheses of the [5,7,5]- and
[5,8,5]-tricyclic ethers and amines which demonstrated the utility of our strategy for the quick and efficient construction of complex polycyclic targets.

**Experimental Section**

**Methoxydodec-11-en-6-yn-1-ol dicobalt hexacarbonyl complex (25).** A 25-mL pear flask containing enyne 24 (159 mg, 0.76 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. Dichloromethane (2 mL) was added, followed by dicobalt octacarbonyl (310 mg, 0.907 mmol, 1.2 equiv). The reaction was stirred for 30 min, and a second portion of dicobalt octacarbonyl (103 mg, 0.302 mmol, 0.4 equiv) was added. After another 30 minutes the reaction mixture was applied directly to a 38 g silica gel column eluted with 25-50% diethyl ether in petroleum ether to afford 334 mg (89%) of 25 as a dark red oil: IR (neat) 3387, 3081, 2936, 2863, 2088, 2040, 1993, 1642 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.85 (ddt, J = 18.5, 11.9, 6.6 Hz, 1H), 5.08 (dd, J = 17.0, 1.3 Hz, 1H), 5.02 (br d, J = 9.9 Hz, 1H), 4.26 (dd, J = 9.0, 3.5 Hz, 1H), 3.68 (q, J = 6.0 Hz, 2H), 3.52 (s, 3H), 2.84 (m, 2H), 2.33-2.25 (m, 2H), 1.88-1.51 (m, 7H), 1.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.1, 137.9, 115.4, 99.1, 98.3, 81.1, 62.7, 58.7, 37.1, 33.9, 32.5, 31.8, 30.4, 25.8.

**2-(But-3-enyl)oxon-3-yne dicobalt hexacarbonyl complex (26).** A 25-mL flask containing cobalt-complexed alkyne 25 (228 mg, 0.46 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. Dichloromethane (20 mL) was added, the reaction flask was cooled at 0 °C, and boron trifluoride diethyl etherate (58 μL, 0.46 mmol, 1.0 equiv) was added. The reaction was stirred for 30 min then quenched by addition of 20 mL saturated sodium bicarbonate. The organic layer was removed and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried with magnesium sulfate and added to a sintered glass funnel filled with silica gel and eluted with 10% diethyl ether in petroleum ether until the first red band was collected and concentrated to yield 91 mg (43%) of 26 as a dark red oil: IR (neat) 3080, 2934, 2859, 2088, 2045, 2014, 1642, 1609 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.87 (m, 1H), 5.04 (m, 2H), 4.40 (m, 1H), 3.97-3.46 (m, 2H), 3.28-2.89 (m,
2H), 2.40-2.20 (m, 2H), 1.93-1.53 (m, 4H), 1.32-1.18 (m, 3H), 0.87 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 200.1, 138.2, 115.3, 37.8, 34.8, 31.7, 30.4, 30.1, 29.8, 29.5, 27.8, 25.9, 25.2.

3,4,5,6,8a,9,10,10a-Octahydro-2H-pentaleno[1,6-bc]oxonin-7(8H)-one (27 + 28).

**Acetonitrile:** To a 25-mL round-bottomed flask containing cobalt complexed alkyne 26 (132 mg, 0.28 mmol, 1.0 equiv) was added acetonitrile (27 mL). The flask was equipped with a reflux condenser, left open to the air, and heated at reflux (100 °C) for 20 min. The reaction mixture was then cooled to room temperature, added to a sintered glass funnel containing 5 g silica gel and 5 g celite, and rinsed with ethyl acetate. The filtrate was concentrated to yield 78 mg (136%) of crude products 27 and 28. The crude product was deposited on 150 mg silica gel and added to a 6 g silica gel column eluted with 20% diethyl ether in petroleum ether to afford 21 mg (19%) of 27 and 28 as a viscous oil with a ratio of 27:28 of 12:1.

**N-methylmorpholine-N-oxide (NMO):** A 50-mL three-necked flask equipped with a rubber septum, glass stopper, and gas inlet adapter was charged with the cobalt-complexed alkyne 26 (142 mg, 0.31 mmol, 1.0 equiv) and dichloromethane (12 mL). The flask was cooled at 0 °C, NMO (108 mg, 0.92 mmol, 3.0 equiv) was added, and the reaction was warmed to room temperature. After 45 min, the reaction was again cooled at 0 °C and another portion of NMO (108 mg) was added. The reaction mixture was warmed to room temperature and stirred for 45 min. This process of cooling at 0 °C, adding NMO (108 mg) and stirring at room temperature for 45 min, was repeated a third time. TLC indicated that the reaction had gone to completion so the reaction mixture was added to a sintered glass funnel filled with celite and rinsed with dichloromethane. The filtrate was washed with water and saturated sodium bicarbonate, filtered, and concentrated to yield 70 mg (111%) of a yellow oil. The crude product was applied neat to a 7 g silica gel column eluted with 25% diethyl ether in petroleum ether to afford 17 mg (27%) of 27 as a colorless film: IR (neat) 2961, 2926, 2855, 1731 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.38 (t, $J = 7.3$ Hz, 1H), 4.08 (dt, $J = 12.4$, 5.3 Hz, 1H), 3.70 (m, 1H), 3.01 (br m, 1H), 2.69 (dd, $J = 17.8$, 6.0 Hz, 1H), 2.63 (dt, $J = 14.6$, 4.4 Hz, 1H), 2.50 (m, 1H), 2.22-2.13 (m, 2H),
2.03 (dd, \( J = 17.9, 3.3 \) Hz, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.65-1.51 (m, 3H), 1.40 (m, 2H), 1.01 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 211.2, 181.8, 136.0, 71.8, 65.9, 43.1, 42.1, 35.1, 29.2, 29.0, 25.2, 22.5, 19.5; HRMS-FAB \( m/z \) [M+H]\(^+\) calcd for C\(_{13}\)H\(_{19}\)O\(_2\) 207.1391, found 207.1385.

**N-(6-methoxydec-9-en-4-ynyl)-4-methylbenzenesulfonamide.** A 50-mL two-necked flask equipped with a rubber septum and gas inlet adapter was charged with (fluorenyl)methyl tosylcarbamate\(^24\) (320 mg, 0.81 mmol, 1.5 equiv), triphenylphosphine (428 mg, 1.63 mmol, 3.0 equiv), and THF (4 mL), and cooled at 0 °C. A separate 25-mL pear flask was charged with alcohol 10 (99 mg, 0.54 mmol, 1.0 equiv) and 2 mL THF. This solution was transferred into the reaction flask via cannula followed by a 1 mL THF rinse. Diethylazadicarboxylate (232 mg, 1.36 mmol, 2.5 equiv) was added to the reaction flask, and the reaction was allowed to stir overnight. The reaction mixture was concentrated to yield 1.27 g (737%) of a yellow oil. The crude product was deposited on 4 g silica gel and added to a 35 g column eluted with 25% diethyl ether in petroleum ether to yield 206 mg (118%) of the target amine as a yellow oil, which was determined to be 90% pure based on the \(^1\)H NMR and was used without further purification in the subsequent cobalt complexation step: IR (neat) 3283, 3073, 2822, 2976, 2249, 1748, 1640, 1598 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.72 (dt, \( J=8.4, 1.8 \) Hz, 2H), 7.30 (d, \( J=8.1 \) Hz, 2H), 5.78 (m, 1H), 5.01 (dq, \( J=17.0, 1.7 \) Hz, 1H), 4.96 (dm, \( J=10.2 \) Hz, 1H), 4.53 (br s, 1H), 3.87 (tt, \( J=6.4, 1.9 \) Hz, 1H), 3.32 (s, 3H), 2.42 (s, 3H), 2.26 (td, \( J=7.0, 1.8 \) Hz, 2H), 2.14 (m, 2H), 1.76-1.64 (m, 3H), 1.34-1.19 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.5, 137.8, 137.0, 130.0, 127.3, 115.2, 85.0, 80.0, 70.7, 56.3, 42.3, 34.9, 29.5, 28.5, 21.6, 16.1.

**N-(6-methoxydec-9-en-4-ynyl)-4-methylbenzenesulfonamide dicobalt hexacarbonyl complex (39).** A 25-mL pear flask containing the amine resulting from Mitsunobu reaction of alcohol 10 (92 mg, 0.28 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. Dichloromethane (2 mL) was added, followed by dicobalt octacarbonyl (115 mg, 0.34 mmol, 1.2 equiv). The reaction was stirred for 30 min, and a second portion of dicobalt octacarbonyl (38 mg, 0.11 mmol, 0.4 equiv) was added. After another 30 minutes the reaction mixture was added to an 18 g silica gel column and eluted...
with 25% diethyl ether in petroleum ether yielded 160 mg (90%) of 39 as a dark red oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J$=8.4 Hz, 2H), 7.30 (d, $J$=7.7 Hz, 2H), 5.84 (m, 1H), 5.04 (m, 2H), 4.43 (m, 1H), 4.42 (m, 1H), 3.48 (s, 3H), 2.81 (m, 1H), 2.25 (m, 2H), 1.78 (m, 4H), 1.25 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 199.9, 143.7, 137.8, 136.8, 129.9, 127.2, 115.6, 98.4, 97.6, 81.1, 58.8, 43.0, 37.1, 31.8, 31.0, 30.3, 21.6.

2-But-3-enyl-1-(toluene-4-sulfonyl)-3-azepyne dicobalt hexacarbonyl complex (40). A 25-mL flask containing cobalt-complexed alkyne 39 (135 mg, 0.22 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. Dichloromethane (14 mL) was added, the reaction flask was cooled at 0 °C, and boron trifluoride diethyl etherate (27 μL, 0.22 mmol, 1.0 equiv) was added. The reaction was stirred at 0 °C for 1.5 h then quenched by addition of 20 mL saturated sodium bicarbonate. The organic layer was removed and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried with magnesium sulfate and added to a sintered glass funnel filled with silica gel and eluted with 5-20% diethyl ether in petroleum ether until the solution ran clear and concentration afforded 93 mg (73%) of 40 as a dark red oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J$= 8.4 Hz, 2H), 7.29 (d, $J$= 8.1 Hz, 2H), 5.58 (m, 1H), 5.19 (t, $J$= 7.3 Hz, 1H), 4.91 (m, 2H), 4.05 (m, 1H), 3.71 (m, 1H), 3.26 (m, 1H), 2.97 (m, 1H), 2.79 (m, 1H), 2.41 (s, 3H), 2.04 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.34 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 199.9, 143.3, 138.8, 136.8, 129.7, 126.9, 115.7, 110.0, 98.6, 95.8, 45.3, 34.8, 34.3, 31.3, 30.1, 21.6.

1-Tosyl-1,2,3,4,6a,7,8,8a-octahydropentaleno[1,6-bc]azepin-5(6H)-one (42).

Cyclohexylamine: A 20-mL round-bottomed flask containing Nicholas product 40 (93 mg, 0.16 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. 1,2-Dimethoxyethane (5.5 mL) was added followed by cyclohexylamine (27 μL, 0.24 mmol, 1.5 equiv). The rubber septum was replaced with a reflux condenser and gas inlet adapter and the reaction was heated at 60 °C for 3 h. The heat was removed and the reaction was allowed to stir over night. The reaction mixture was added to a sintered glass funnel filled with celite and washed with ethyl acetate (50 mL) to yield 59 mg (113%) of a
yellow oil. The crude product was applied directly to a 6 g silica gel column and eluted with 30% diethyl ether in petroleum ether to yield 51 mg (98%) of 42 as a colorless viscous oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.71 (d, \(J = 8.4\) Hz, 2H), 7.28 (d, \(J = 8.1\) Hz, 2H), 5.17 (t, \(J = 8.4\) Hz, 1H), 3.70 (dt, \(J = 15.4, 3.7\) Hz, 1H), 2.91 (m, 1H), 2.81 (m, 1H), 2.65 (dd, \(J = 18.3, 6.6\) Hz, 1H), 2.40 (s, 3H), 2.35-2.17 (m, 4H), 2.06 (dd, \(J = 18.7, 2.2\) Hz, 1H), 1.88 (m, 1H), 1.71 (m, 2H), 1.26 (m, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 209.1, 178.7, 143.5, 137.8, 135.7, 129.9, 127.1, 57.9, 43.7, 42.6, 38.9, 31.6, 29.9, 26.6, 21.6, 18.8; HRMS-FAB \(m/z\) [M-H]+ calcd for C\(_{18}\)H\(_{20}\)NO\(_3\)S 330.1164, found 330.1153.

8-Methoxydodec-11-en-6-ynoic acid.\(^{27,28}\) A 25-mL two-necked flask equipped with a rubber septum and gas inlet adapter was charged with Dess-Martin periodinane (520 mg, 1.23 mmol, 1.2 equiv) and dichloromethane (4.5 mL). A separate 25-mL pear flask containing alcohol 24 (215 mg, 1.02 mmol, 1.0 equiv) in 1.0 mL dichloromethane was cannulated into the reaction flask followed by a dichloromethane (0.5 mL) rinse. The reaction mixture was stirred at room temperature for 1 h, diluted with 15 mL diethyl ether, and transferred to an Erlenmeyer flask containing 15 mL of a saturated sodium bicarbonate solution and 3 g of sodium thiosulfate, and stirred for 5 min. The organic layer was washed with 50 mL of saturated sodium bicarbonate, 50 mL of water, dried with magnesium sulfate, filtered, and concentrated to yield 176 mg (83%) of the desired aldehyde as a yellow oil: IR (neat) 3076, 2937, 2863, 2821, 2721, 2227, 1725, 1641 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 9.77 (m, 1H), 5.81 (ddt, \(J = 17.0, 10.4, 6.6\) Hz 1H), 5.03 (dd, \(J = 17.2, 1.5\) Hz, 1H), 4.95 (dd, \(J = 10.2, 1.1\) Hz, 1H), 3.92 (tt, \(J = 6.6, 1.8\) Hz, 1H), 3.38 (s, 3H), 2.46 (td, \(J = 7.3, 1.6\) Hz, 2H), 2.26 (td, \(J = 7.0, 1.5\) Hz, 2H), 2.18 (q, \(J = 7.3\) Hz, 2H), 1.76 (m, 4H), 1.56 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.3, 137.8, 115.0, 85.7, 79.2, 70.8, 56.2, 43.3, 35.0, 29.5, 28.1, 21.2, 18.5; HRMS-FAB \(m/z\) [M-H]+ calcd for C\(_{13}\)H\(_{19}\)O\(_2\) 207.1385, found 207.1404.

A 50-mL round-bottomed flask containing the previous prepared aldehyde (123 mg, 0.59 mmol, 1.0 equiv) was equipped with a rubber septum and gas inlet needle. Dimethylformamide (7 mL) was added followed by Oxone (363 mg, 0.59 mmol, 1.0 equiv) and the reaction was stirred at room temperature for
two hours. The reaction mixture was added to a separatory funnel containing ethyl acetate (30 mL) and 1.0 M hydrochloric acid (30 mL). The aqueous layer was removed and extracted with 50 mL ethyl acetate, and the combined organic layers were washed with 1.0 M hydrochloric acid (5 x 50 mL) and brine (50 mL), dried with magnesium sulfate, filtered, and concentrated to yield 143 mg (108%) of the desired carboxylic acid as a yellow oil that was used without further purification: IR (neat) 3077, 2937, 2867, 2650, 2230, 1711, 1648, cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.81 (ddt, $J$ = 17.2, 10.2, 6.6 Hz, 1H), 5.04 (dq, $J$ = 17.0, 1.8 Hz, 1H), 4.97 (dm, $J$ = 11.0 Hz, 1H), 3.92 (tt, $J$ = 6.6, 1.8 Hz, 1H), 3.38 (s, 3H), 2.94 (d, $J$ = 30.4 Hz, 3H), 2.38 (t, $J$ = 7.5 Hz, 2H), 2.26 (td, $J$ = 7.0, 1.9 Hz, 2H), 2.20 (m, 2H), 1.76 (m, 4H), 1.57 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.1, 137.9, 115.1, 85.9, 79.1, 70.8, 56.2, 35.0, 33.6, 29.5, 28.1, 23.9, 18.5; HRMS-FAB m/z [M-H]$^+$ calcd for C$_{13}$H$_{19}$O$_3$ 223.1334, found 223.1351.

8-Methoxydodec-11-en-6-ynoic acid dicobalt hexacarbonyl complex (61). According to the general procedure, combination of the carboxylic acid resulting from oxidation of alcohol 24 (52 mg, 0.23 mmol, 1.0 equiv), dichloromethane (1 mL), and dicobalt octacarbonyl (95 mg, 0.28 mmol, 1.2 equiv) then 31 mg, 0.09 mmol, 0.4 equiv) followed by direct addition to a 12 g silica gel column and eluted with 15-100% diethyl ether in petroleum ether yielded 62 mg (52%) of 61 as a dark red oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.8 (br s, 1H), 5.85 (m, 1H), 5.05 (m, 2H), 4.27 (m, 1H), 3.48 (s, 3H), 2.86 (br s, 2H), 2.26 (m, 2H), 1.79 (m, 6H), 1.28 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.1, 137.8, 115.5, 98.3, 81.1, 67.0, 58.8, 37.1, 33.7, 30.4, 22.4, 15.3, 14.2.

9,18-Dibut-3-enyl-1,10-dioxacyclooctadeca-7,16-diyne-2,11-dione dicobalt hexacarbonyl complex (62). According to the general procedure, combination of cobalt-complexed alkyne 61 (62 mg, 0.12 mmol, 1.0 equiv), dichloromethane (6 mL), and tetrafluoroboric acid (54% in diethyl ether, 17 $\mu$L, 0.12 mmol, 1.0 equiv) at 0 ºC for 1 h followed by the aqueous workup and addition to a sintered glass funnel filled with silica gel and eluted with 10% diethyl ether in petroleum ether until the solution ran clear and concentration afforded 10 mg (9%) of 62 as a dark red oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.03
(m, 2H), 5.84 (m, 2H), 5.03 (m, 4H), 2.80 (m, 4H), 2.55-2.19 (m, 6H), 2.01-1.54 (m, 14H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.7, 172.5, 137.1, 125.6, 115.7, 99.3, 72.8, 35.8, 34.3, 33.3, 31.5, 30.2, 25.2.

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Supporting Information Available. General experimental details, materials, references to compounds previously reported in the literature, experimental procedures for all new compounds, 1D $^1$H NMR spectra for compounds 20-33, 39-47, 51, and 61-62, and difference NOE and COSY spectra for 27, 28, 42. This material is available free of charge via the Internet at http://pubs.acs.org.

References.

1 For a review, see Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. Topics in Organometallic Chemistry 2006, 19, 259-294.

2 For a review of tandem Nicholas/Pauson-Khand reactions, see Pérez-Castells, J. Topics in Organometallic Chemistry 2006, 19, 207-257.


9 For a communication from our lab containing several examples of endocyclic intramolecular Nicholas reactions with alcohol nucleophiles, see reference 4a.


12 For a preliminary report from our lab detailing inter- and intramolecular Nicholas reactions with carboxylic acid nucleophiles, see reference 4b.


18 The diastereomeric ratios for all Pauson-Khand products were determined by 1H NMR. Major and minor isomers were assigned using COSY and difference NOE NMR experiments.

19 Results for all of the Pauson-Khand conditions are available in reference 4a.


21 This is a known compound, see Marino, J. P.; Nguyen, H. N. J. Org. Chem. 2002, 67, 6291-6296.


The structure of cobalt-alkyne complex 55 was not unambiguously assigned by NMR spectroscopy because the material was used immediately in the subsequent Nicholas reaction. Due to the similarity in TLC behavior to all of the other cobalt-alkyne complexes prepared in our lab, we are confident that 55 was successfully synthesized.

The structure of diolide 56 could not be unambiguously assigned by NMR spectroscopy due to the presence of paramagnetic cobalt impurities even after purification by column chromatography. We are confident in the formation of this compound due to the similar TLC behavior and general ¹H NMR features (very broad peaks) in comparison to diolides 59 and 62.

The structure of the trans isomer of 59 was confirmed by X-ray single crystal analysis; see reference 4b.
