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Nitrous Oxide Promoted Pauson−Khand Cycloadditions

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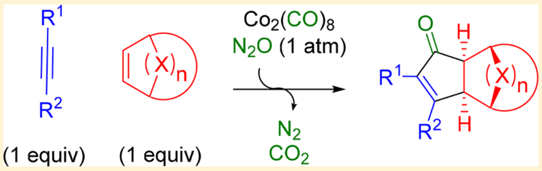
Supporting Information

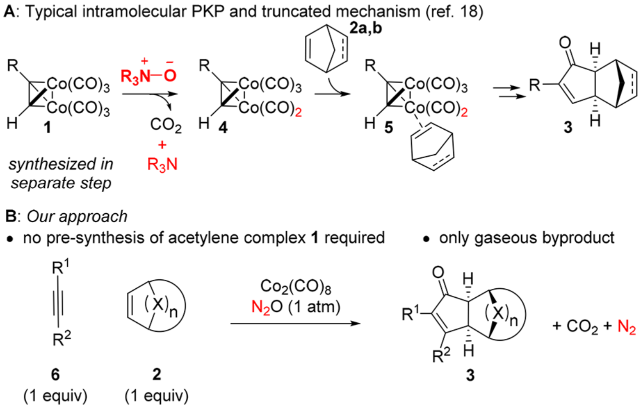
ABSTRACT: A Pauson−Khand cycloaddition of alkynes, alkenes, and carbon monoxide promoted by cobalt carbonyl and nitrous oxide to furnish cyclopentenones is described. Preliminary mechanistic experiments suggest that nitrous oxide functions in a manner similar to that of the *N*-oxide promoters typically employed in Pauson−Khand reactions. Only dinitrogen and carbon dioxide are produced as a consequence of the activation mechanism, thus avoiding high-molecular-weight reagents and the buildup of basic byproducts. The chemistry is done using equimolar amounts of alkyne, alkene, and dicobalt octacarbonyl and is performed directly from the acetylenic component without the need to presynthesize a cobalt-alkyne complex. Terminal acetylenes were suitable substrates, as was solid calcium carbide, and the corresponding adducts were isolated in good yields. Furthermore, two sequential [4 + 3] and [2 + 2+1] cycloadditions were performed, generating functionalized cyclopentenones in only two steps from readily available starting materials.



The Pauson−Khand reaction (PKR) is a [2 + 2 + 1] cycloaddition among an alkyne, an alkene, and carbon monoxide to yield cyclopentenones.[1] It was first discovered in the early 1970s as a stoichiometric reaction between acetylenedicobalt hexacarbonyl (**1a**; R = H) and norbornene (**2a**) at elevated temperatures to yield the cycloadduct in moderate yield.[2]

The accepted mechanism (Scheme 1A)[3] was proposed on the basis of the observed regiochemistry of **3a** and has been largely supported by DFT calculations[4] and mass spectrometry.[5] After formation of the dicobalt acetylene complex **1**, dissociation of a molecule of CO from **1** to form **4** must occur so that an alkene can coordinate to generate **5**, which goes on to form the cyclopentenone product **3**. The most common method for the formation of **4** is the application of a promoter, typically amine *N*-oxides.[6] The amine *N*-oxide is required to be used in 5−10-fold excess to get synthetically useful yields of the cyclopentenone adducts,[7] generating a substantial amount of waste. Thus, it is somewhat surprising that the simplest *N*-oxide, nitrous oxide (N_2O), has never been used as a promoter in this reaction. Replacing the commonly employed trimethylamine *N*-oxide (TMAO) with N_2O reduces the amount of waste generated. Moreover, nitrous oxide is inexpensive and widely available, yet there are few applications of the gas as a reagent in chemical synthesis.[8] Most transition-metal-catalyzed or -mediated processes that currently utilize N_2O involve direct transfer of the oxygen atom of N_2O to the transition-metal center.[9] However, we hypothesized that, if N_2O could oxidize the CO ligand rather than cobalt,[10] we could promote the PKR and avoid the need for large excesses of solid oxide promoters (Scheme 1B).

Scheme 1. Summary of Cobalt-Mediated Pauson−Khand Cycloadditions



We began the study by comparing the isolated yields of cyclopentenone **3b** when the cycloaddition was performed in the presence of 1 equiv of $Co_2(CO)_8$ either with 1 equiv of a solid *N*-oxide promotor or in the presence of N_2O at 40 °C in acetonitrile (Table 1). We found that at that loading TMAO was an effective promoter of the PKR (entry 1), but *N*-methylmorpholine *N*-oxide (NMO) required higher loading in accordance with previously reported studies[7] (entry 2 vs entry 3) to be effective. Nicotinamide *N*-oxide (NNO) was ineffective, and **3b** was produced in low yields among other unidentifiable materials (entry 4). We were pleased to note that performing the PKR in an N_2O-saturated acetonitrile solution gave cyclopentenone **3b** in 80% yield after 20 h (entry 5). Extending the reaction time to 24 h improved the isolated yield of **3b** to 86% (entry 6). Performing the reaction at room temperature led to a slight reduction in the isolated yield of **3b** (entry 7); performing the reaction in the total absence of promoter led to only a trace amount of **3b** (entry 8). We

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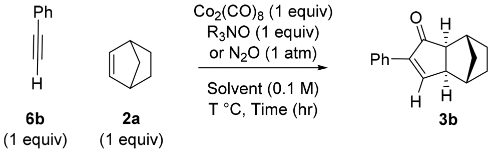
Table 1. Selected Optimization Experiments in the N_2O-Mediated PKR[a]



entry	R_3NO	solvent (0.1 M)	T (°C)	t (h)	yield of **3a** (%)[a]
1	TMAO	MeCN	40	20	69
2	NMO	MeCN	40	20	29
3	NMO[b]	MeCN	40	20	75
4	NNO	MeCN	40	24	intractable mixture
5	N_2O	MeCN	40	20	80
6	**N_2O**	**MeCN**	**40**	**24**	**86**
7	N_2O	MeCN	20	24	64
8		MeCN	40	24	trace
9	N_2O	toluene	40	24	74
10	N_2O	DME	40	24	10
11	N_2O	THF	40	24	77
12	N_2O	DCM	40	24	40
13	N_2O	$CHCl_3$	40	24	52

[a]Yields are of material isolated by silica gel chromatography. [b]6 equiv of NMO. See the Supporting Information for further details.

attempted to further improve the yield of the cycloadduct by varying the solvent (entries 8–12), but the reaction performed best in MeCN.

To determine whether N_2O was in fact acting in a manner analogous to that of other *N*-oxides, we compared in situ FTIR data for the reaction between the cobalt phenylacetylene hexacarbonyl complex **1b** and both TMAO and N_2O. The generation of CO_2 was observed at 2338 cm^{-1} upon addition of each promoter, though rapid outgassing of the solution prevented kinetic analysis of the two processes (Figure 1). While production of CO_2 is consistent with the oxidative extrusion of a CO ligand from the hexacarbonyl intermediate **1b** and formation of the putative pentacarbonyl species **4b**, we cannot rule out a more complex role for N_2O at this time.

We then turned to examining the scope of the alkyne component in the reaction (Table 2, top). To synthesize the parent cyclopentenone, we opted to use the solid reagent calcium carbide (**6a**) rather than gaseous acetylene to avoid concurrent introduction of two gaseous reagents. Calcium carbide, though exceedingly inexpensive, is not often employed as an acetylene surrogate.[11] We were pleased to note that CaC_2 was an effective substrate when it was used with 2 equiv of water, and the cyclopentenone **3a** was isolated in good yield.[12] Phenylacetylene **6b** was an excellent substrate, giving cyclopentenone **3b** in high yield. Electronically different species, whether electron rich (**6c**) or electron poor (**6d,e**) were somewhat less effective, and products **3c–e** were isolated in somewhat lower yields. The internal alkyne dimethyl acetylenedicarboxylate **6f** was an excellent substrate, and the product **3f** was isolated in good yield. Other functional groups were well tolerated, and cyclopentenones containing coordinative alcohol and nitrile functional groups, **3h,i**, were isolated in good yields. Norbornadiene was also an effective partner in the PKR,[13] and adducts **3j–l** were isolated in generally good yield.

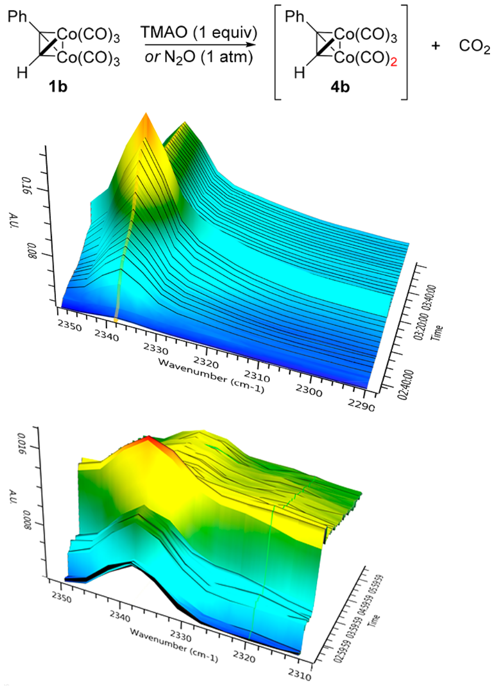
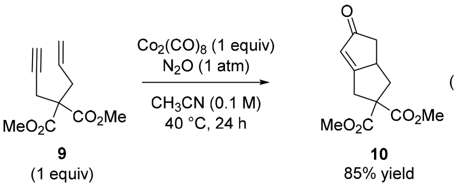


Figure 1. In situ FTIR data comparing the activation of the cobalt phenylacetylene complex **1b** (top) as promoted by TMAO (middle) and N_2O (bottom). The *x*-axis shows the region of CO_2 absorbance, and the *z*-axis begins at the addition of the *N*-oxide.

The intermolecular PKR is typically limited to either olefins with a low LUMO or those that possess a pendant Lewis base for secondary coordination to cobalt but otherwise contain little functionality.[7,14] We were interested in applying more functionalized alkenes to the PKR. The [3.2.1] and [3.2.2] bicyclic olefins **8a–c** were particularly interesting, as they are easily constructed from cyclic butadienes and ureas via [4 + 3] cycloadditions[15] and contain many synthetic handles for downstream transformations. We thus subjected bridged bicyclic alkenes **8a–c** to our standard conditions. Though not as strained as the [2.2.1] bicyclic alkenes,[16] these olefins were ready participants in the PKR, and densely functionalized cyclopentenones **3m–o** were produced in good yields (Table 2, bottom). All cyclopentenones were isolated as single isomers, and exo selectivity was determined by comparing acquired spectral data to those of the known compounds **3a,b,f–h,j–l** and extrapolating them to those of the unknown compounds **3c–e,i,m–o**.

Finally, we demonstrated the applicability of these reaction conditions to the cyclization of a 1,6-enyne (eq 1). The malonate derivative **9** smoothly reacted with $Co_2(CO)_8$ in the presence of N_2O to give the [5.5] bicyclic compound **10** in high yield (89%).



(eq 1)

In conclusion, N_2O has been used for the first time as a promoter in the Pauson–Khand reaction. Its use avoids the buildup of basic waste in situ that other often used promoters (NMO, TMAO) leave behind. We have preliminary evidence that N_2O oxidatively removes a CO ligand from the cobalt complex, but more detailed mechanistic explorations are

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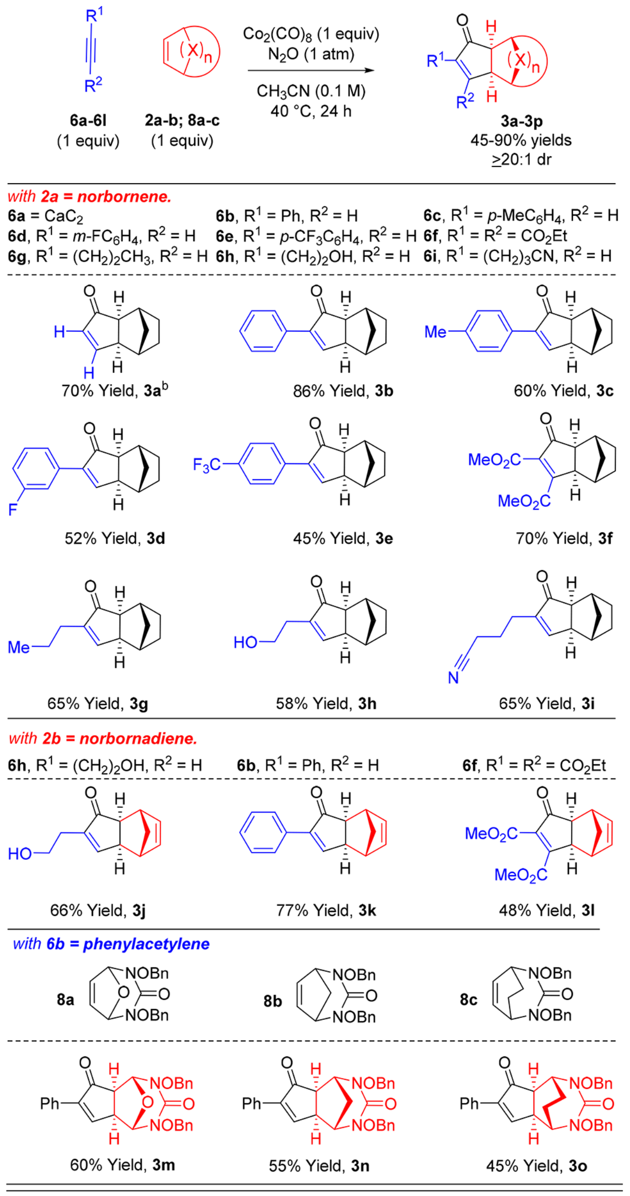
Table 2. Scope of the Intermolecular PKR between Alkynes 1a–i and Norbornene 2a As Promoted by Nitrous Oxide[a]



[a]Yields are of material isolated by silica gel chromatography. [b]2 equiv of H_2O was added. See Supporting Information for further details

warranted. We found that N_2O promoted the cycloaddition between alkynes and bridged bicyclic olefins in moderate to good yields and that the reaction could be executed directly from the alkyne with no need to presynthesize the cobalt alkyne complex. Our application of sequential [4 + 3] and [2 + 2 + 1] cycloadditions combines inexpensive and readily available starting materials to give complex, densely functionalized tricyclic ring systems in only two steps.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00810.

Experimental details and ^{1}H and ^{13}C NMR, HRMS, and elemental analyses of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *The Pauson–Khand reaction. Scope, variations and applications*; Wiley: 2012. (b) Ricker, J. D.; Geary, L. M. Recent advances in the Pauson–Khand reaction. *Top. Catal.* **2017**, *60*, 609–619.

(2) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. Organocobalt complexes. Part II. Reaction of acetylenehexacarbonyldicobalt complexes, $(R_1C_2R_2)Co_2(CO)_6$, with norbornene and its derivatives. *J. Chem. Soc., Perkin Trans. 1* **1973**, *1*, 977–981.

(3) Magnus, P.; Principe, L. M. Origins of 1,2- and 1,3-stereoselectivity in dicobaltcarbonyl alkene-alkyne cyclizations for the synthesis of substituted bicyclo[3.3.0]octenones. *Tetrahedron Lett.* **1985**, *26*, 4851–4854.

(4) (a) Yamanaka, M.; Nakamura, E. Density functional studies on the Pauson–Khand reaction. *J. Am. Chem. Soc.* **2001**, *123*, 1703–1708. (b) de Bruin, T. J. M.; Michel, C.; Vekey, K.; Greene, A. E.; Gimbert, Y.; Milet, A. First C-C bond formation in the Pauson–Khand reaction: Influence of carbon-carbon triple bond polarization on regiochemistry. A density functional theory study. *J. Organomet. Chem.* **2006**, *691*, 4281–4288.

(5) (a) Gimbert, Y.; Lesage, D.; Milet, A.; Fournier, F.; Greene, A. E.; Tabet, J.-C. On early events in the Pauson–Khand reaction. *Org. Lett.* **2003**, *5*, 4073–4075. (b) Henderson, M. A.; Luo, J.; Oliver, A.; McIndoe, J. S. The Pauson–Khand reaction: A gas-phase and solution-phase examination using electrospray ionization mass spectrometry. *Organometallics* **2011**, *30*, 5471–5479. (c) Lesage, D.; Milet, A.; Memboeuf, A.; Blu, J.; Greene, A. E.; Tabet, J.-C.; Gimbert, Y. The Pauson–Khand mechanism revisited: Origin of CO in the final product. *Angew. Chem., Int. Ed.* **2014**, *53*, 1939–1942.

(6) CO dissociation can also occur thermally or photochemically, though these methods are less commonly used.

(7) Gibson, S. E.; Mainolfi, N. The intermolecular Pauson–Khand reaction. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037.

(8) Severin, K. Synthetic chemistry with nitrous oxide. *Chem. Soc. Rev.* **2015**, *44*, 6375–6386.

(9) (a) Tskhovrebov, A. G.; Solari, E.; Scopelliti, R.; Severin, K. Activation of nitrous oxide by dinuclear ruthenium complexes. *Organometallics* **2012**, *31*, 7235–7240. (b) Tskhovrebov, A. G.; Solari, E.; Wodrich, M. D.; Scopelliti, R.; Severin, K. Sequential N-O and N-N bond cleavage of *N*-heterocyclic carbene-activated nitrous oxide with a vanadium complex. *J. Am. Chem. Soc.* **2012**, *134*, 1471–1473. (c) Gianetti, T. L.; Rodríguez-Lugo, R. E.; Harmer, J. R.; Trincado, M.; Vogt, M.; Santiso-Quinones, G.; Grützmacher, H. Zero-valent amino-olefin cobalt complexes as catalysts for oxygen atom transfer reactions from nitrous oxide. *Angew. Chem., Int. Ed.* **2016**, *55*, 15323–15328.

(10) There are limited examples of CO oxidation by N_2O; for an example, see: Bottomley, F.; Lin, I. J. B.; Mukaida, M. Reactions of dinitrogen oxide (nitrous oxide) with dicyclopentadienyltitanium

complexes including a reaction in which carbon monoxide is oxidized. *J. Am. Chem. Soc.* **1980**, *102*, 5238−5242.

(11) Rodygin, K. S.; Werner, G.; Kucherov, F. A.; Ananikov, V. P. Calcium carbide: a unique reagent for chemical synthesis. *Chem. - Asian J.* **2016**, *11*, 965−976.

(12) When gaseous acetylene was used in conjunction with N_2O, a more complex reaction outcome was observed by TLC.

(13) Aiguabella, N.; Pesquer, A.; Verdaguer, X.; Riera, A. Pauson−Khand Adducts of *N*-Boc-propargylamine: A New Approach to 4,5-Disubstituted Cyclopentenones. *Org. Lett.* **2013**, *15*, 2696−2699.

(14) Though there have been a few examples of simple endocyclic olefins used in PKR, these olefins are typically used in large excess, and the conditions are generally harsh.

(15) Anumandla, D.; Littlefield, R.; Jeffrey, C. S. Oxidative 1,4-diamination of dienes using simple urea derivatives. *Org. Lett.* **2014**, *16*, 5112−5115.

(16) Fishman, J. M.; Kiessling, L. L. Synthesis of functionalizable and degradable polymers by ring-opening metathesis polymerization. *Angew. Chem., Int. Ed.* **2013**, *52*, 5061−5064.

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