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Increased Yields and Simplified Purification with a Second-Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings

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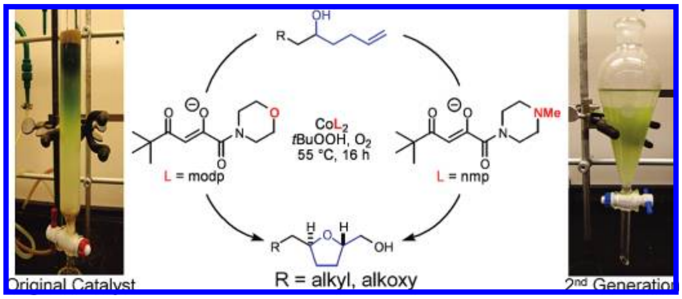
ABSTRACT



The synthesis of a second-generation cobalt catalyst for the formation of *trans*-THF products via the Mukaiyama aerobic oxidative cyclization is reported. Two procedures have been developed with the new water-soluble catalyst that give superior yields and greatly simplify purification compared to the previous catalysts.

The ubiquitous nature of tetrahydrofuran (THF) rings in a wide variety of biologically active natural products has inspired the development of methods for their synthesis and derivatization.[1] In particular, the ability to form 2,5-*trans*-THF rings in an efficient and diastereoselective manner is essential for the synthesis of many natural products displaying this structural motif. Many methods have been utilized to access *trans*-THF rings. However, some methods have poor yields or low diastereoselectivities.[2] The Mukaiyama aerobic oxidative cyclization is emerging as a powerful synthetic tool that uses molecular oxygen as the stoichiometric oxidant to convert pentenols to *trans*-THF rings (Scheme 1).[3] The reaction has been the subject of mechanistic investigations[4] and has also been utilized in total synthesis (Figure 1).[5] Our research group has applied this strategy in the total synthesis of aplysiallene[6] and bullatacin.[7] Herein, we report our success in the development of a second-generation cobalt catalyst for the formation

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(1) (a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460. (c) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271–284.

(2) For reviews see: (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408. (b) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290. (c) Li, N.; Shi, Z.; Tang, T.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* **2008**, *4*.

(3) Inoki, S; Mukaiyama, T. *Chem. Lett.* **1990**, *1*, 67–70.

(4) (a) Pérez, B. M.; Schuch, D.; Hartung, J. *Org. Biomol. Chem.* **2008**, *6*, 3532–3541. (b) Schuch, D.; Fries, P.; Donges, M.; Pérez, B. M.; Hartung, J. *J. Am. Chem. Soc.* **2009**, *131*, 12918–12920.

(5) (a) Wang, Z.-M.; Tian, S.-K. ; Shi, M. *Tetrahedron Lett.* **1999**, *40*, 997–980. (b) Tian, S.-K.; Wang, Z.-M.; Jiang, J.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2551–2562. (c) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 667–670. (d) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Eur. J. Org. Chem.* **2000**, *2*, 349–356. (e) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Chirality* **2000**, *12*, 581–587. (f) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703.

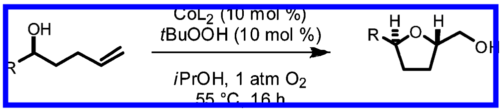
(6) Wang, J.; Pagenkopf, B. L. *Org. Lett.* **2007**, *9*, 3703–3706.

(7) Zhao, H.; Gorman, J. S. T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379–4382.

10.1021/ol9023375

of *trans*-THF rings that gives superior yields and greatly simplifies purification when compared to the standard catalysts.

Scheme 1. Representative Mukaiyama Aerobic Oxidative Cyclization



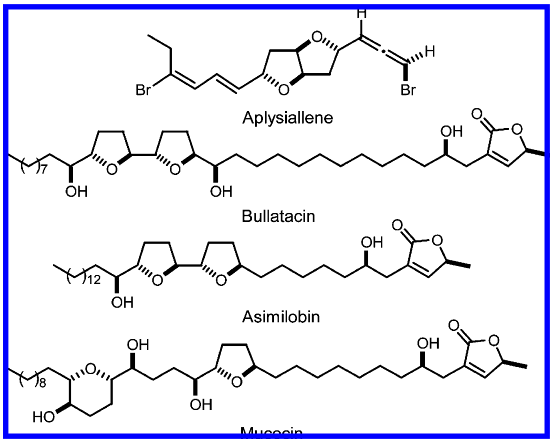


Figure 1. Natural products containing *trans*-THF rings synthesized using the Mukaiyama oxidation.[8]

The Mukaiyama oxidation typically proceeds in good yield and excellent diastereoselectivity (>99:1 dr); however, in some cases, the catalyst was extraordinarily difficult to remove from the desired THF product when the standard ligands **1** and **2** (Figure 2) were utilized.[9] Furthermore, paramagnetic cobalt residues interfere with NMR analysis, making characterization of the cyclized product difficult or impossible. The difficulties associated with purification detract from the synthetic advantages of the catalyst. Thus, we set out to prepare a new catalyst that retains high efficiency but also exhibits significantly increased polarity. This and related strategies have seen great success with EDC, water-soluble ligands, sulfonated phosphines, fluorous phases, and ionic liquids.[10] Using the well-established modp ligand **1** as a template, it was envisioned that replacing the neutral morpholine subunit with a basic *N*-methyl piperazine (**3**, 5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione, henceforth nmp) might facilitate removal of the cobalt species from the reaction mixture by a straightforward acidic extraction.

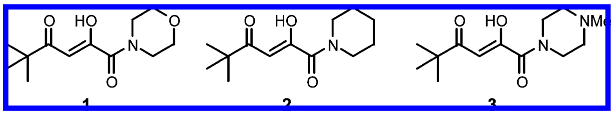


Figure 2. Commonly used modp (**1**) and piper (**2**) ligands and water-soluble nmp (**3**).

The synthesis of the nmp ligand commenced with reaction of *N*-methyl piperazine with ethyl oxalyl chloride in the presence of triethylamine, which proceeded in near quantitative yield (Scheme 2). A significant loss of product was observed (ca. 50%) when the subsequent Claisen condensation of **4** with pinacolone was subjected to a standard aqueous workup.[7] Fortuitously, an alternative protonation method employing acetic acid in CH_2Cl_2 followed by removal of the salts by filtration afforded ligand **3** in 95% yield. Complexation of the nmp ligand **3** with Co(ethyl-2-hexanoate)$_2$ in dry benzene was initially low yielding, and the resulting purple-colored solid performed poorly in subsequent cyclization reactions. Previously, we reported the first X-ray structures of these types of catalysts that clearly showed adventitious water in the crystal structure.[11] Complexation in aqueous benzene provided Co(nmp)$_2$ (**5**) as a tan-

Scheme 2. Synthesis of Co(nmp)$_2$

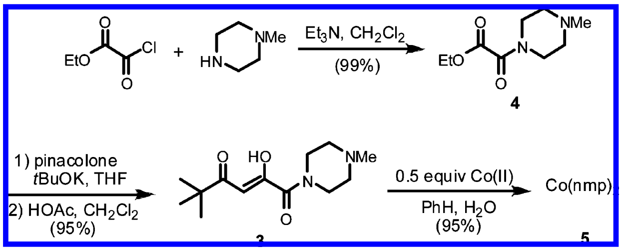
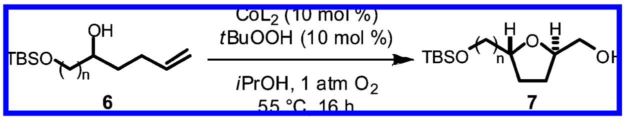


Table 1. Initial Comparison of the Catalysts



entry	starting material	*n*	yield (%) modp	piper	nmp buffer[a]	nmp MeI
1	**6a**	1	65	39	92	93
2	**6b**	2	68	75	90	90
3	**6c**	3	79	74	92	95

[a] pH 4 phosphate buffer.

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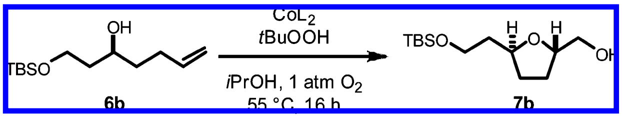
(8) For aplysiallene, see ref 6. For bullatacin, see ref 7. For asimilobin, see ref 5a. For mucocin, see ref 5f.

(9) See Supporting Information for photographs showing elution of cobalt residues.

(10) (a) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525–2528. (b) Herrmann, W. A.; Kulpe, J. A.; Konkol, W.; Bahrmann, H. *J. Organomet. Chem* **1990**, *389* (1), 85–101. (c) Water-soluble ligands: Herrmann, W. A.; Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524–1544. (d) Curran, D. P. *Aldrichimica Acta* **2006**, *39*, 3–9.

(11) Wang, J.; Morra, N. A.; Zhao, H.; Gorman, J. S. T.; Lynch, V.; McDonald, R.; Reichwein, J. F.; Pagenkopf, B. L. *Can. J. Chem.* **2009**, *87*, 328–334. The actual molecular formula is most likely [{Co(nmp)$_3$}$_2$Co(H_2O)$_6$] but is represented as Co(nmp)$_2$ for simplicity.

Table 2. Effect of Catalyst Loadings on the Oxidation of **6b**



entry	catalyst	mol %	yield (%)
1	Co(modp)$_2$	15	68
2	Co(modp)$_2$	10	65
3	Co(modp)$_2$	5	47[a]
4	Co(nmp)$_2$	15	95
5	Co(nmp)$_2$	10	97
6	Co(nmp)$_2$	5	93
7	Co(nmp)$_2$	3	57 (93)[b]
8	Co(nmp)$_2$	1	10 (77)[b]

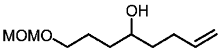
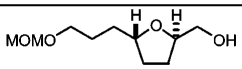
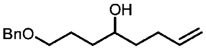
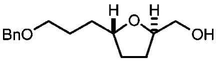
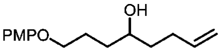
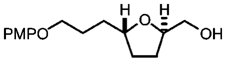
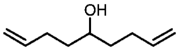
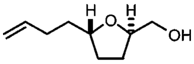
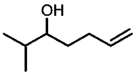
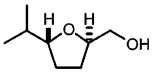
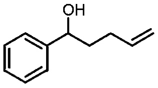
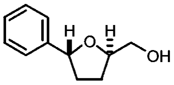
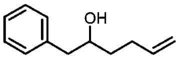
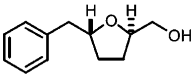
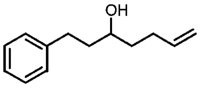
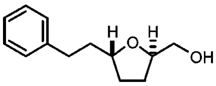
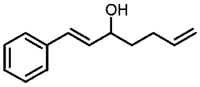
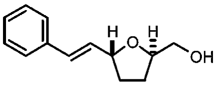
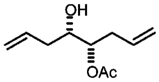
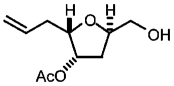
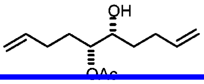
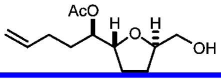
[a] All starting material was consumed. [b] Yield based on recovered starting material.

colored solid in 89% yield over three steps, using benchtop centrifugation as the only method of purification to collect the catalyst. Gratifyingly, the oxidation results with the Co(nmp)$_2$ catalyst formed under aqueous conditions proved to be exceptional (vide infra).

To compare the new Co(nmp)$_2$ catalyst to previous ones (Co(modp)$_2$ and Co(piper)$_2$), a family of TBS-protected pentenol derivatives that have proven to be reliable substrates in these reactions were selected (Table 1). Encouragingly, these early results with Co(nmp)$_2$ demonstrated a remarkable improvement in the overall yield of the oxidative cyclization process. These new conditions also circumvent the undesired side reactions leading to aldehydes and protocyclization products, typically observed with traditional catalysts.[4]

With regards to product purification, it is important to note that when using the Co(nmp)$_2$ catalyst system complete removal of the cobalt residues from the *trans*-THF products was achieved easily with pH 4 phosphate buffer wash of the organic layer. Anticipating the need for a neutral workup procedure to remove the catalyst from more acid-sensitive substrates, the

Table 3. Cyclization Precursors and Their Respective Cyclized Products

			yield (%)			
					Co(nmp)$_2$	
entry[a]	starting Material	product	Co(piper)$_2$	Co(modp)$_2$	MeI	buffer
1[b]			69[d]	64[d]	85	54
2[b]			20	58	90	66
3[b]			29	81[d]	90	85
4			46	57	95	40
5			62	76	91	58
6			54	47	91	45
7			52	70	90	60
8			71[d]	49	86	80
9			38	42	88	46
10[c]			55	81[e]	83	78
11[c]			69	79[f]	88	79

[a] Typical reaction conditions: cyclization precursor (1 equiv), Co(nmp)$_2$ (10 mol %), *t*BuOOH (10 mol %), *i*PrOH (10 mL), O$_2$ (1 atm), 55 °C. [b] Racemic material. [c] Enantiomerically pure. [d] This yield is for a mixture of THF product contaminated with cobalt species that could not be removed after repeated chromatography. Thus, the yield is artificially elevated. [e] See ref 6. [f] See ref 7.

tertiary amine was quaternized by treating the reaction mixture with MeI under an argon atmosphere. The resulting salts are highly water soluble and can be removed using a simple neutral water extraction. The new Co(nmp)$_2$ catalyst system facilitates a mild and straightforward isolation and purification process, and when coupled with the improved yields, it greatly enhances the synthetic potential of this methodology.

The effect of catalyst loading on cyclization efficiency was investigated (Table 2). The typical catalyst loading reported for Co(modp)$_2$ cyclizations is 10 mol %. In the oxidation of **6b** (Table 2), the yield did not improve significantly at higher loading (entry 1), while with lower catalyst loading the yield dropped significantly (entry 3). Gratifyingly, it was observed that reactions using Co(nmp)$_2$ proceeded efficiently with catalyst loadings as low as 5 mol % (entries 4−6), while lower loadings resulted in incomplete conversion (entries 7 and 8). It is noteworthy that with Co(modp)$_2$ at 5 mol % catalyst loading byproduct formation becomes seriously competitive, but these side reactions are not observed with catalyst loading as low as 3 mol % with the new Co(nmp)$_2$ system (compare entries 3 with 6 and 7).

Encouraged by the results with Co(nmp)$_2$ in the initial screening of TBS-protected pentenol derivatives, its performance was compared against the standard cobalt catalysts with a variety of additional substrates (Table 3). In all cases examined, reactions run with the new Co(nmp)$_2$ catalyst resulted in an increased yield compared to the original catalyst. The polar hydrophilic THF (entry 1) was impossible to separate from the Co(modp)$_2$ and Co(piper)$_2$ catalyst residues even after repeated column chromatography with different eluents. In contrast, after in situ methylation of the Co(nmp)$_2$ species, the THF product was obtained in pure form in 85% yield after an aqueous extraction. The results in entries 2 and 3 were equally satisfying, and it is noteworthy that the oxidatively labile benzyl and *p*-methoxyphenyl ether protecting groups survive the reaction conditions.[12] A symmetric pentadienol (entry 4), in addition to sterically encumbered substrates (entries 5 and 6), was also found to readily cyclize under the oxidation conditions. Furthermore, aromatic substrates including phenyl, benzyl, and cinnamic acid derivatives all gave favorable results (entries 6−9, respectively). Finally, the compounds in entries 10 and 11 are intermediates that were employed in the total synthesis of aplysiallene[6] and bullatacin,[7] respectively, thus further illustrating the overall superiority and utility of this new catalyst for natural product synthesis.

In summary, a second-generation catalyst for the Mukaiyama oxidative cyclization is reported. The catalyst preparation is straightforward at gram scale with centrifugation as the only means of purification. In all cases examined, cyclization reactions using Co(nmp)$_2$ have shown improved yields and fewer side products. Most importantly, Co(nmp)$_2$ has greatly simplified postreaction purification by replacing difficult column chromatography with an aqueous workup. We believe this new second-generation catalyst now clearly stands among the best methods to prepare 2,5-disubstituted *trans*-THF rings, and it is sure to find applications in total synthesis.

Acknowledgment. We thank the University of Western Ontario and the National Sciences and Engineering Research Counsil of Canada for financial asistance. N.M. (NSERC CGS D) and B.B. (Vanier CGS) thank NSERC for their graduate fellowships. We also thank James Russell Macdonald for experimental assistance.

Supporting Information Available: Experimental procedures and characterization of all new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Previous studies in our laboratory have shown that PMB protective groups are destructively cleaved under the conditions of the oxidative cyclization.