OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

Manganese-Catalyzed Stereospecific Hydroxymethylation of Alkyl Tosylates

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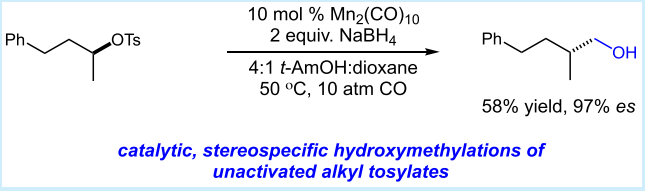
Supporting Information

ABSTRACT: The development of a stereospecific hydroxymethylation of alkyl tosylates using an inexpensive, first-row catalyst is described. The transformation proceeds under mild conditions with low pressure to deliver homologated alcohols as products. Chiral, nonracemic β-branched primary alcohols are obtained with high enantiospecificity from easily accessed secondary alkyl substrates. Simple modification of the reaction system also permits access to α-d_2 alcohols. These studies use anionic metal carbonyl catalysis to access a synthetic equivalent of the challenging hydroxymethyl anion from carbon monoxide.



The homologation of carbon chains by a single unit is featured in a number of synthetic organic reactions. Classic transformations of carbonyl compounds such as the Killiani–Fisher and Arndt–Eistert syntheses are valued for their simplicity and convenience and find widespread use in synthesis.[1−7] Conversely, few methods are available for the formal homologation of alcohols, either directly or via their conversion to alkyl halides or pseudohalides.[8,9] Recent work has demonstrated the potential of radical-mediated methods to achieve this goal (Figure 1). For example, Ryu and co-workers

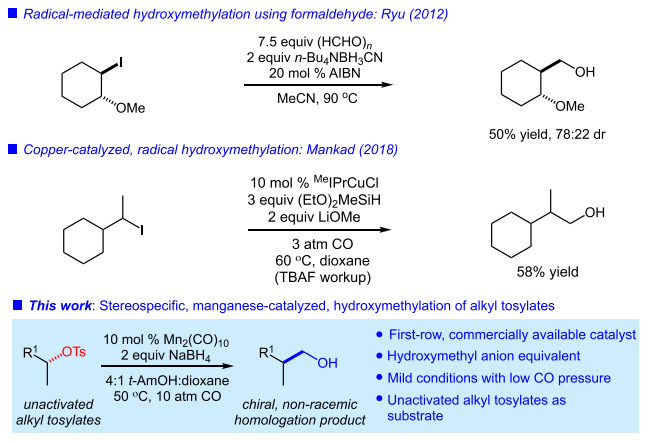


Figure 1. Hydroxymethylations of alkyl electrophiles.

have developed a hydromethylation using formaldehyde and cyanoborohydride in a radical chain process.[10] More recently, Mankad and co-workers reported a copper-catalyzed, radical-mediated transformation of alkyl iodides to silyl ethers, which upon deprotection with tetrabutylammonium fluoride yields homologated alcohols.[11] In each of these processes, the intermediacy of carbon-centered radicals dictates that stereocontrol in reactions of secondary substrates is a significant challenge.

We targeted the development of an alternative, stereospecific approach to the homologation of alkyl electrophiles using anionic metal carbonyl catalysis.[12] Chiral, nonracemic branched primary alcohols are important building blocks in asymmetric synthesis. This strategy would facilitate their synthesis from easily accessed, chiral, nonracemic secondary alkyl tosylates. Herein, we report the successful development of a stereospecific hydroxymethylation using a commercially available manganese carbonyl dimer. This mild, catalytic transformation represents a unique and concise approach to the one carbon homologation of alkyl tosylates with excellent stereocontrol.

Our investigation commenced with the hydroxymethylation of primary tosylate **1** (Table 1). We determined that a catalytic system comprising 10 mol % $Mn_2(CO)_{10}$ and two equivalents of $NaBH_4$ provided the homologated alcohol **2** in good yield (67%, entry 1). Substitution of $Mn_2(CO)_{10}$ with the putative catalytic nucleophile $Na[Mn(CO)_5]$ was similarly effective (entry 2). Interestingly, the use of $Co_2(CO)_8$—the precatalyst used in previous studies of stereospecific anionic metal carbonyls catalysis—significantly reduced reaction efficiency, likely owing to the lower nucleophilicity of $Na[Co(CO)_4]$ (entry 3).[12,13] Decreasing the catalyst loading to 5 mol % (entry 4) or the CO pressure to 1 atm (balloon, entry 5) slightly lowered efficiency. Increasing the CO pressure to 20 atm provided little improvement (entry 6). Performing the reaction at room temperature decreased conversion (entry 7), while excluding ambient light had little effect (entry 8). Notably, omitting the dioxane cosolvent did not impact the yield in this case, but was important with other tosylates (entry

Received: October 19, 2019

DOI: 10.1021/acs.orglett.9b03706
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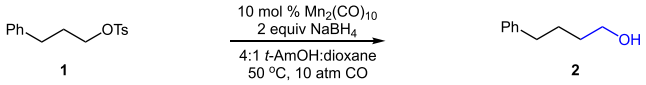
Table 1. Manganese-Catalyzed Hydroxymethylation of an Unactivated Alkyl Tosylate*



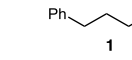
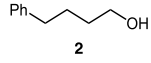
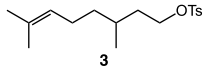
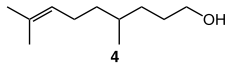
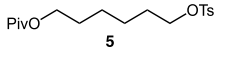
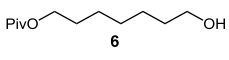
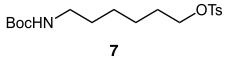
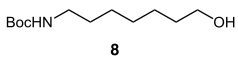
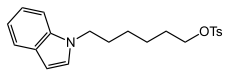
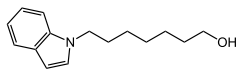
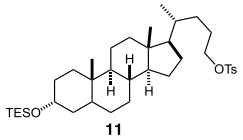
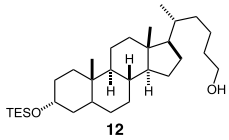
entry	variation from standard conditions above	yield (%)[a]
1	none	67
2	20 mol % $Na[Mn(CO)_5]$	68
3	10 mol % $Co_2(CO)_8$	50
4	5 mol % $Mn_2(CO)_{10}$	61
5	1 atm CO	60
6	20 atm CO	70
7	rt	48
8	dark	64
9	no dioxane	66
10	no $Mn_2(CO)_{10}$	0

*Reactions were performed with $[\mathbf{1}]_0$ = 0.5 M. [a]Yields determined by ^{1}H NMR spectroscopy of crude reaction mixture using an internal standard.

9).[14] No product was formed in the absence of the catalyst (entry 10).

Having identified a viable catalytic system, we turned our attention to the scope of the hydroxymethylation, starting with primary alkyl tosylates (Table 2). The hydroxymethylation of

Table 2. Manganese-Catalyzed Hydroxymethylation of Primary Alkyl Tosylates

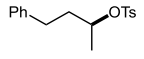
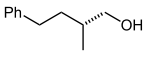
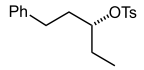
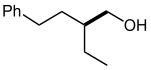
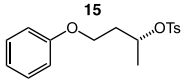
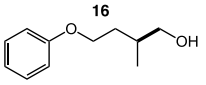
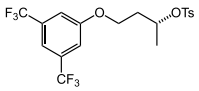
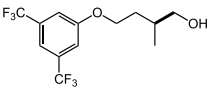
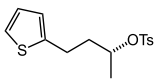
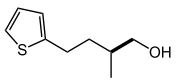
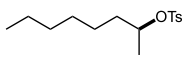
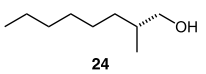
entry	substrate	product	yield (%)[a]
1	 1	 2	66
2	 3	 4	52
3	 5	 6	57
4	 7	 8	53
5	 9	 10	58
6	 11	 12	56

*See Table 1 for conditions. [a]Isolated yields.

the tosylate derived from the monoterpenoid citronellol provided homologated alcohol **4**, demonstrating compatibility with alkenyl substrates (entry 2). Common polar functionality such as esters and Boc-protected amines are also tolerated in the hydroxymethylation (entries 3 and 4). The homologation of indolyl tosylate **9** yielded alcohol **10**, demonstrating the efficiency of the reaction in the presence of electron-rich heterocycles (entry 5). Notably, the hydroxymethylation of a lithocholic acid derivative is successful in the presence of a silyl ether, which would undergo deprotection using a previously reported copper-catalyzed hydroxymethylation protocol (entry 6).[11]

We continued with the hydroxymethylations of chiral, nonracemic secondary tosylates (Table 3). We view the

Table 3. Stereospecific, Manganese-Catalyzed Hydroxymethylation of Chiral, Nonracemic Secondary Alkyl Tosylates*

entry	substrate	product	yield (%)[a]	es (%)
1	 13	 14	58[b]	97
2	 15	 16	40[b]	>99
3	 17	 18	48	95
4	 19	 20	50	94
5	 21	 22	52	99
6	 23	 24	47	87[c]

*See Table 1 for conditions. [a]Isolated yields unless otherwise noted. Enantiospecificity (*es*) = ($ee_{product}/ee_{substrate}$) × 100%, determined by chiral HPLC. [b]Reaction yield determined by ^{1}H NMR spectroscopy of crude reaction mixtures using an internal standard. [c]Enantiospecificity determined from the tosylated product (see Supporting Information).

capability of our polar catalytic manifold to enable stereospecific hydroxymethylations as a powerful, unique aspect of our approach. The hydroxymethylation of chiral, nonracemic tosylate **13** delivered alcohol **14** in 58% yield and with excellent enantiospecificity (97%, entry 1). Importantly, the reaction is not limited to methyl-branched substrates as demonstrated by the reaction of tosylate **15**, which although less efficient (40% ^{1}H NMR yield, 31% isolated yield) proceeds in >99% es (entry 2). The homologations of tosylates derived from chiral, nonracemic 1,3-diols proceeded efficiently with high enantiospecificities (entries 3 and 4) and demonstrated reaction tolerance of electron-poor arenes. Alkyl tosylate **21** containing thiophene underwent hydroxymethylations in 54% yield. Finally, a simple aliphatic tosylate (**23**) was also a viable substrate and provided the hydroxymethylation product with good enantiospecificity (entry 6). In general, the mass balance was a mixture of unreacted starting material, elimination, or reduction byproducts. While the results of Tables 2 and 3 demonstrate that the reaction yields of the hydroxymethylation are moderate, the uniformly high stereoselectivities are an attractive feature of this catalytic process.

α-Deuterated alcohols are important compounds due to their use as drug analogs and internal standards in proteomic, metabolomic, and LADMET studies.[15] Common routes to these α-deuterated products proceed via reduction of

DOI: 10.1021/acs.orglett.9b03706
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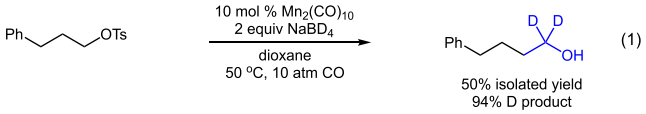
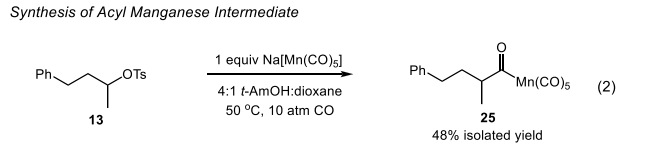
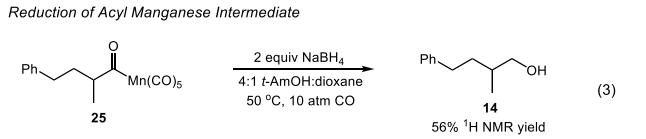
carboxylic acid derivatives using $LiAlD_4$ or highly reactive single-electron reductants.[16] An alternative approach via direct α-deuteration of an alcohol requires precious ruthenium catalysts and can provide product regioisomers.[17−19] Given its commercial availability, we sought to apply $NaBD_4$ in the hydroxymethylation to achieve α-deuterium incorporation under our mild catalytic conditions. As an initial demonstration of our approach to α-deuterated alcohols, we performed the hydroxymethylation of primary tosylate **1** with 2 equiv of $NaBD_4$. The hydroxymethylation proceeded in 50% isolated yield and 94% deuterium incorporation (eq 1). This



modification of our catalytic system involves a nucleophilic substitution with a formal deuterated hydroxymethyl anion equivalent and offers a new concise approach to α-deuterated alcohols under mild conditions.

We sought to uncover details regarding the reaction mechanism by studying the reactivity of a putative acylmanganese intermediate. The reaction of substrate **13** with 1 equiv of $Na[Mn(CO)_5]$—the active catalyst formed *in situ*—in the absence of $NaBH_4$ provided the acylmanganese **25** in 48% yield. This intermediate was subsequently reduced with $NaBH_4$ to deliver the homologated alcohol **14** in 56% ^{1}H NMR yield (eq 3), consistent with the viability of



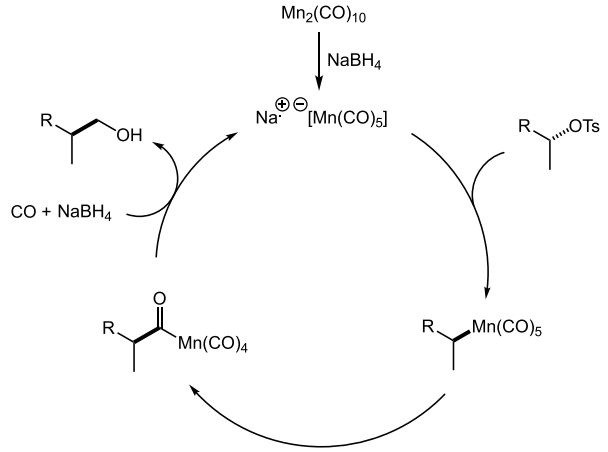


acylmanganese as a precursor to the hydroxymethylation product. Furthermore, comparison of hydroxymethylation product **14** (Table 3, entry 1) to an independently prepared sample indicated that the reaction proceeded with inversion of configuration at the stereogenic center.

A mechanistic proposal for the catalytic hydroxymethylation is illustrated in Scheme 1. The dimanganese decacarbonyl precatalyst is reduced *in situ* by $NaBH_4$ to provide the active sodium pentacarbonylmanganate species. Subsequent nucleophilic attack on the substrate forms an alkylmanganese intermediate, which undergoes migratory insertion of CO with retention of configuration. The resulting acyl manganese is reduced by $NaBH_4$ to regenerate the active catalyst. The aldehyde initially formed in this step is further reduced to give the hydroxymethylation product.

In conclusion, we have developed a stereospecific hydroxymethylation of alkyl tosylates using manganese catalysis. This approach leverages the reactivity of anionic metal carbonyl catalysis to access a formal hydroxymethyl anion equivalent from CO and hydride. A mild, stereospecific homologation of alkyl electrophiles is achieved, providing direct access to chiral, nonracemic β-branched primary alcohols—and α-deuterated derivatives—from simple starting materials. Future studies will target the further development of valuable synthetic methods using this unique mode of metal catalysis.

Scheme 1. Plausible Catalytic Cycle for Stereospecific Hydroxymethylation



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03706.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported under award number R35 GM131708 from the National Institute of General Medical Sciences. We thank the UNC Department of Chemistry Mass Spectrometry Core Laboratory for assistance with MS analysis, supported by the National Institute of General Medical Sciences under award number R35 GM118055 and the National Science Foundation under award number CHE 1726291. We thank Justin Marcum (University of North Carolina—Chapel Hill) for assistance with SFC and helpful discussions.

■ REFERENCES

(1) Kowalski, C. J.; Haque, M. S.; Fields, K. W. Ester Homologation Via Alpha-Bromo Alpha-Keto Dianion Rearrangement. *J. Am. Chem. Soc.* **1985**, *107*, 1429−1430.

(2) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981−10080.

(3) Levine, S. G. A New Aldehyde Synthesis. *J. Am. Chem. Soc.* **1958**, *80*, 6150−6151.

DOI: 10.1021/acs.orglett.9b03706
Org. Lett. XXXX, XXX, XXX−XXX

(4) Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. A One-Carbon Homologation of Carbonyl Compounds to Carboxylic Acids, Esters, and Amides. *J. Am. Chem. Soc.* **1977**, *99*, 182−186.
(5) Kluge, A. F.; Cloudsdale, I. S. Phosphonate Reagents for the Synthesis of Enol Ethers and One-Carbon Homologation to Aldehydes. *J. Org. Chem.* **1979**, *44*, 4847−4852.
(6) McNulty, J.; Das, P. Development of A One-Pot Method for the Homologation of Aldehydes to Carboxylic Acids. *Tetrahedron* **2009**, *65*, 7794−7800.
(7) Cukalovic, A.; Monbaliu, J.-C. M.; Heynderickx, G. J.; Stevens, C. V. User Friendly and Flexible Kiliani Reaction on Ketoses Using Microreaction Technology. *J. Flow Chem.* **2012**, *2*, 43−46.
(8) Kagawa, N.; Nibbs, A. E.; Rawal, V. H. One-Carbon Homologation of Primary Alcohols to Carboxylic Acids, Esters, and Amides via Mitsunobu Reactions with MAC Reagents. *Org. Lett.* **2016**, *18*, 2363−2366.
(9) Soundararajan, R.; Li, G.; Brown, H. C. Homologation of Representative Boronic Esters Using in situ Generated (Halomethyl)-lithiums: A Comparative Study. *Tetrahedron Lett.* **1994**, *35*, 8957−8960.
(10) (a) Kawamoto, T.; Fukuyama, T.; Ryu, I. Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator. A New Protocol for Hydroxymethylation Reaction. *J. Am. Chem. Soc.* **2012**, *134*, 875−877. (b) For an earlier example of radical-mediated hydroxymethylation, see: Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. Black-Light-Induced Radical/Ionic Hydroxymethylation of Alkyl Iodides with Atmospheric CO in the Presence of Tetrabutylammonium Borohydride. *Org. Lett.* **2013**, *12*, 1548−1551.
(11) Zhao, S.; Mankad, N. Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO to Provide One-Carbon-Extended Alcohols. *Angew. Chem., Int. Ed.* **2018**, *57*, 5867−5870.
(12) For prior work in stereospecific carbonylation of alkyl tosylates, see: (a) Sargent, B. T.; Alexanian, E. J. Cobalt-Catalyzed Carbonylative Cross-Coupling of Alkyl Tosylates and Dienes: Stereospecific Synthesis of Dienones at Low Pressure. *J. Am. Chem. Soc.* **2017**, *139*, 12438−12440. (b) Sargent, B. T.; Alexanian, E. J. Cobalt-Catalyzed Aminocarbonylation of Alkyl Tosylates: Stereospecific Carbonylation of Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 9533−9536.
(13) King, R. B. Applications of Metal Carbonyl Anions In The Synthesis of Unusual Organometallic Compounds. *Acc. Chem. Res.* **1970**, *3*, 417−427.
(14) See the Supporting Information for a representative example of the effect of dioxane.
(15) Michelotti, A.; Roche, M. 40 Years of Hydrogen−Deuterium Exchange Adjacent to Heteroatoms: A Survey. *Synthesis* **2019**, *51*, 1319−1328.
(16) Szostak, M.; Spain, M.; Procter, D. J. Electron Transfer Reduction of Unactivated Esters Using SmI_2−H_2O. *Chem. Commun.* **2011**, *47*, 10254−10256.
(17) Chatterjee, B.; Gunanathan, C. Ruthenium Catalyzed Selective α- and α,β-Deuteration of Alcohols Using D_2O. *Org. Lett.* **2015**, *17*, 4794−4797.
(18) Zhang, L.; Nguyen, D. H.; Raffa, G.; Desset, S.; Paul, S.; Dumeignil, F.; Gauvin, R. M. Efficient Deuterium Labelling of Alcohols in Deuterated Water Catalyzed by Ruthenium Pincer Complexes. *Catal. Commun.* **2016**, *84*, 67−70.
(19) Kar, S.; Goeppert, A.; Sen, R.; Kothandaraman, J.; Prakash, G. K. S. Regioselective Deuteration of Alcohols in D_2O Catalysed by Homogeneous Manganese and Iron Pincer Complexes. *Green Chem.* **2018**, *20*, 2706−2710.

DOI: 10.1021/acs.orglett.9b03706
Org. Lett. XXXX, XXX, XXX−XXX