JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Cobalt-Catalyzed Carbonylative Cross Coupling of Alkyl Tosylates and Dienes: Stereospecific Synthesis of Dienones at Low Pressure

Brendon T. Sargent, and Erik J. Alexanian

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b07983 • Publication Date (Web): 22 Aug 2017

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Cobalt-Catalyzed Carbonylative Cross Coupling of Alkyl Tosylates and Dienes: Stereospecific Synthesis of Dienones at Low Pressure

Brendon T. Sargent and Erik J. Alexanian*

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

Supporting Information Placeholder

ABSTRACT: Despite advances in organometallic cross coupling of alkyl electrophiles, there are few stereoselective reactions of chiral, non-racemic substrates. Herein, we report a stereospecific carbonylative coupling of alkyl tosylates and dienes producing enantioenriched dienones. This catalytic process proceeds under low pressure and mild conditions using a simple cobalt catalyst and extends to diverse tosylate and diene coupling partners. The transformation constitutes a unique, convergent approach to the asymmetric synthesis of valuable carbonyl compounds from easily accessed starting materials.

Catalytic cross couplings of secondary alkyl electrophiles are powerful transformations for the stereoselective construction of C–C bonds.[1] Enantioconvergent transformations of racemic electrophiles facilitate access to an array of important chemotypes, but these transformations often utilize proximal coordinating functionality to promote enantioselective transformations.[2] An alternative, though less common, approach is to utilize chiral, non-racemic electrophiles in stereoselective cross couplings.[3] This approach capitalizes on the array of methods available for preparing simple building blocks stereoselectively (e.g., chiral, non-racemic secondary alcohols).[4] Despite the potential for such processes, they are currently limited in scope.

An early example of a carbonylative, stereoselective cross coupling of a chiral, non-racemic secondary electrophile is the Fe-mediated ketone synthesis developed by Collman (Figure 1).[5] While this strategy extends to a variety of carbonyl compounds, the requirement for stoichiometric $Na_2Fe(CO)_4$, an air and water sensitive, highly reactive reagent, is a significant drawback. Alternatively, anionic cobalt carbonyl complexes have been shown to catalyze several carbonylative processes involving alkyl electrophiles.[6] Stereoselective applications have not appeared, however. We were intrigued by prior reports demonstrating cobalt-catalyzed couplings with dienes, albeit with primary or activated electrophiles.[7] Herein, we report a catalytic, stereospecific carbonylative cross coupling of alkyl electrophiles using an easily accessed anionic cobalt catalyst. This mild, catalytic process enables the stereoselective synthesis of valuable dienones from chiral, non-racemic secondary alkyl tosylates and dienes in a convergent manner.

Our studies commenced with the carbonylative cross coupling of unactivated secondary alkyl tosylate (*S*)-**1** and diene **2** (Table 1). A catalytic system comprised of 10 mol % $K[Co(CO)_4]$ and 1.1 equiv of TMP (2,2,6,6-tetramethylpiperidine) provided dienone **3**

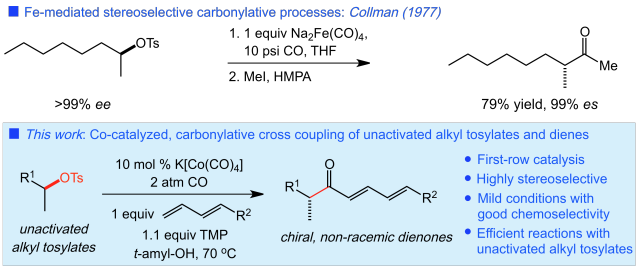
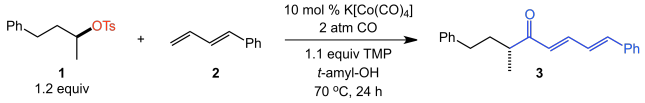


Figure 1. Stereospecific, carbonylative cross couplings of alkyl tosylates.

in good yield and enantiospecificity (84% ^{1}H NMR yield, 93% *es*, entry 1). Substituting 10 mol % $Na[Co(CO)_4]$ (entry 2) or 5 mol % of the dimeric $Co_2(CO)_8$ as catalyst (entry 3) led to decreased yield. A palladium-based catalytic system we previously used in the esterification of unactivated secondary alkyl bromides provided no product (entry 4).[8] Lowering the catalyst loading to 5 mol % (entry 5) had a minor effect on chemical yield. Decreasing the CO pressure to 1 atm (entry 6) led to decreased reaction conversion and enantiospecificity. The use of higher pressures of CO (5 atm, entry 7) provided no improvement over 2 atm CO. The inorganic base Cs_2CO_3 was inferior to the organic base TMP and completely racemized the product (entry 8). Reaction in the absence of ambient light proceeded with only a slight decrease in yield and enantiospecificity (78% ^{1}H NMR yield, 90% *es*, entry 9),[7d] and no reaction occurred in the absence of catalyst (entry 10).

Table 1. Cobalt-catalyzed cross coupling of an unactivated alkyl tosylate with a terminal diene.

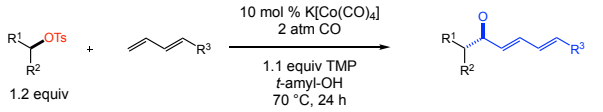


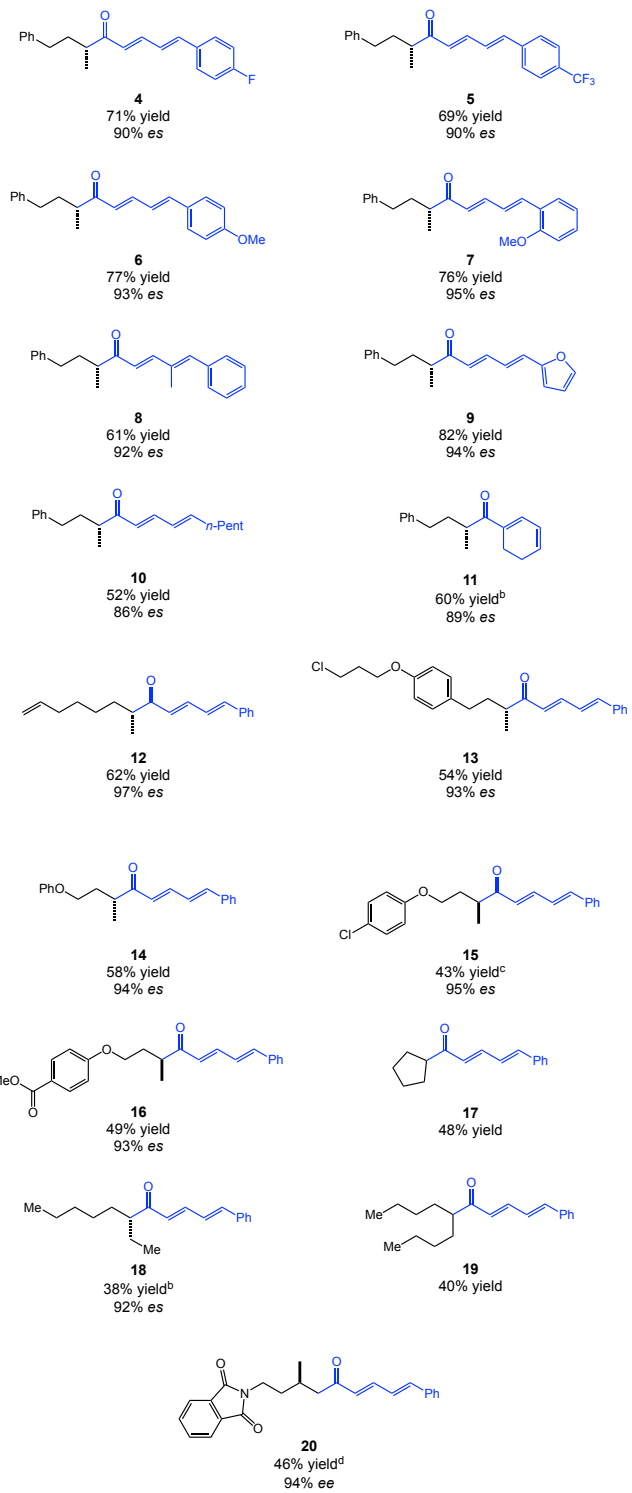
entry	variation from standard conditions above	yield (%)[a]	*es* (%)[b]
1	(*S*)-**1**	84	93
2	10 mol % $Na[Co(CO)_4]$ instead of $K[Co(CO)_4]$	62	91
3	5 mol % $Co_2(CO)_8$ instead of $K[Co(CO)_4]$	72	94
4	5 mol % $Pd(PPh_3)_2Cl_2$/10 mol % IMes instead of $K[Co(CO)_4]$	< 2	
5	5 mol % instead of 10 mol % $K[Co(CO)_4]$	67	93
6	1 atm (balloon) CO instead of 2 atm CO	53	70
7	5 atm CO instead of 2 atm CO	84	90
8	Cs_2CO_3 instead of TMP	36	4
9	no ambient light	78	90
10	no $K[Co(CO)_4]$	< 2	

Reactions were performed with $[2]_0$ = 0.5 M. [a]Yields determined by ^{1}H NMR spectroscopy of crude reaction mixture using an inter-

nal standard. [b]Enantiospecificity (*es*) = ($ee_{product}/ee_{substrate}$) x 100%, determined by chiral HPLC.

Table 2. Stereospecific, low-pressure catalytic cross couplings of alkyl tosylates and dienes.[a]



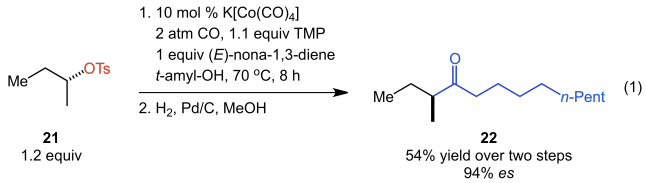


See Table 1 for conditions. [a]Isolated yields unless otherwise noted. Enantiospecificity (*es*) = ($ee_{product}/ee_{substrate}$) x 100%, determined by chiral HPLC. [b]Reaction yield determined by ^{1}H NMR spectroscopy of crude reaction mixtures using an internal standard. [c]Reaction time 16 h. [d]Reaction performed at 10 atm CO and 90 °C.

We next applied the catalytic system to the carbonylative cross couplings of a range of dienes using (*S*)-**1** as substrate (Table 2). Electron-rich and electron-poor dienes were well tolerated under the reaction conditions (**4**-**7**). In addition, cross coupling with a substituted diene provided dienone **8** in good yield. The carbonylative cross couplings of heterocyclic dienes and aliphatic dienes also proceeded efficiently (**9**-**10**). Importantly, the reaction is not limited to acyclic dienes, as the coupling with 1,3-cyclohexadiene delivered dienone **11** in 60% yield with good stereocontrol (89% *es*).

An initial survey of diverse chiral, non-racemic alkyl tosylates supports the generality of this method. Pendant functionality including alkenes and alkyl halides were well tolerated providing dienones **12** and **13**, respectively, in good yields and high enantiospecificities. The reactions of substrates derived from enantioenriched 1,3-diols efficiently provided γ-alkoxy dienones with good stereospecificity, and demonstrated tolerance of aryl ester and chloride substitution (**14**-**16**). Cycloalkyl tosylates are also viable coupling partners, as demonstrated by the carbonylative cross coupling of cyclopentyl tosylate (**17**). The reaction is not limited to acyclic secondary tosylates with methyl branching; the transformation of the tosylate of (*S*)-3-octanol yielded **18** with good enantiospecificity (92%) and larger branching groups were tolerated with similar reaction efficiency (**19**). Furthermore, primary tosylates were competent substrates in the reaction, as a phthalimide protected amino alcohol derivative containing an α-chiral center delivered dienone **20** in moderate yield with minimal racemization.

The asymmetric synthesis of non-symmetrical ketones containing α-chiral centers remains a significant synthetic challenge. Common approaches generally involve long linear sequences and the use of chiral auxiliaries, as there are very limited strategies for the asymmetric α-alkylation of ketones.[9] We envisioned a concise, convergent route to these compounds via the stereospecific carbonylative cross coupling of tosylates, followed by simple reduction of the dienone. As an initial demonstration, we targeted naturally occurring ketone **22** (eq 1).[10] The stereospecific coupling of the tosylate of (*R*)-butan-2-ol (**21**) with (*E*)-nona-1,3-diene was followed by hydrogenation to provide ketone **22** in 54% yield over two steps, with 94% *es*. This strategy offers a powerful approach to non-symmetrical ketones with α-chiral centers, capitalizing on the availability of chiral, non-racemic secondary alcohols. Additionally, applications of the product dienones in selective 1,4- or 1,6-conjugate additions, or Diels-Alder cycloadditions, are easily envisioned.[11]

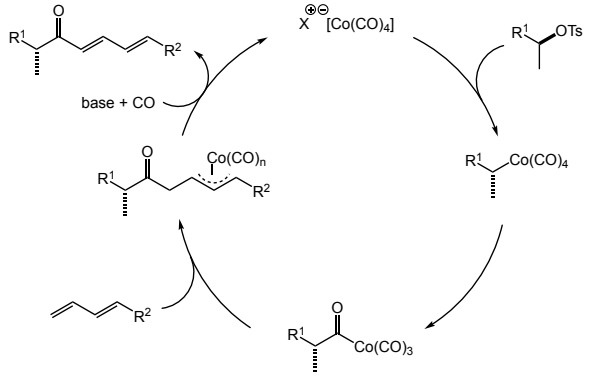


(1)

A mechanistic outline for the carbonylative cross coupling is depicted in Scheme 1. The cobalt catalyst first engages with the

alkyl tosylate in an S_N2 displacement to provide an alkylcobalt intermediate.[12] This species undergoes migratory insertion of CO with retention of configuration, followed by acylmetallation of the diene substrate to provide an allylcobalt. β-hydride elimination or β-elimination of the cobalt yields the dienone product and the catalyst is regenerated.

Scheme 1. Plausible catalytic cycle for the stereospecific, carbonylative cross coupling.



In conclusion, we have developed a stereospecific, carbonylative cross coupling of alkyl tosylates and dienes using a simple cobaltate salt as catalyst. The present work is a rare example of stereospecific, catalytic cross couplings of alkyl electrophiles. This transformation provides expedient access to chiral, nonracemic dienones and derivatives under mild, catalytic conditions. Further efforts to capitalize on the catalytic properties of anionic metal carbonyls in stereospecific processes with alkyl electrophiles are underway.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*eja@email.unc.edu

ACKNOWLEDGMENT

This work was supported by Award No. R01 GM107204 from the National Institute of General Medical Sciences.

REFERENCES

(1) (a) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937. (b) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656. (c) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal.* **2014**, *4*, 2977. (d) Iwasaki, T.; Kambe, N. *Top. Curr. Chem.* **2016**, *374*, 66. For a review on complex natural product syntheses using sp^3-sp^3 cross-couplings, see (e) Geist, E.; Kirschning, A.; Schmidt, T. *Nat. Prod. Rep.* **2014**, *31*, 441.

(2) Choi, J.; Fu, G. C. *Science* **2017**, *356*, eaaf7230.

(3) (a) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799. (b) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344. (c) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083. (d) Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082. (e) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124.

(4) (a) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986. (b) Patel, R. N. *Biomolecules* **2013**, *3*, 741. (c) Collados, J. F.; Solà, R.; Harutyunyan, S. R.; Maciá, B. *ACS Catal.* **2016**, *6*, 1952.

(5) Collman, J. P.; Finke, R. G.; Cawse, J. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 2515.

(6) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 3383.

(7) (a) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 2779. (b) Hegedus, L. S.; Inoue, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4917. (c) Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1984**, *49*, 2570. (d) Kohn, B. L.; Rovis, T. *Chem. Sci.* **2014**, *5*, 2889. (e) Alper, H.; Currie, J. K. *Tetrahedron Lett.* **1979**, *20*, 2665.

(8) Sargent, B. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, 138, 7520.

(9) (a) Krenske, E. H.; Houk, K. N.; Lim, D.; Wengryniuk, S. E.; Coltart, D. M. *J. Org. Chem.* **2010**, *75*, 8578. (b) Clarke, S. L.; McSweeney, C. M.; McGlacken, G. P. *Tetrahedron Asymmetry* **2014**, *25*, 356. For catalytic examples, see: (c) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 3701. (d) Arceo, E.; Bahamonde, A.; Bergonzini, G.; Melchiorre, P. *Chem. Sci.* **2014**, *5*, 2438.

(10) Schulz, S.; Dickschat, J. S.; Kunze, B.; Wagner-Dobler, I.; Diestel, R.; Sasse, F. *Mar. Drugs* **2010**, *8*, 2976.

(11) (a) Amoah, E.; Dieter, R. K. *J. Org. Chem.* **2017**, *82*, 2870. (b) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (c) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1982**, *65*, 2212. (d) Shaw, S.; White, J. D. *Org. Lett.* **2015**, *17*, 4564. (e) Wang, J.; Wang, W.; Liu, X.; Hou, Z.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2011**, 2039. (f) Moriarty, K. Curtin, M. Koyama, K. Roush, W. *J. Am. Chem. Soc.* **1996**, *118*, 7502.

(12) See supporting information for determination of absolute stereochemistry.