Organic LETTERS

Letter

pubs.acs.org/OrgLett

Tunable Aerobic Oxidative Hydroxylation/Dehydrogenative Homocoupling of Pyrazol-5-ones under Transition-Metal-Free Conditions

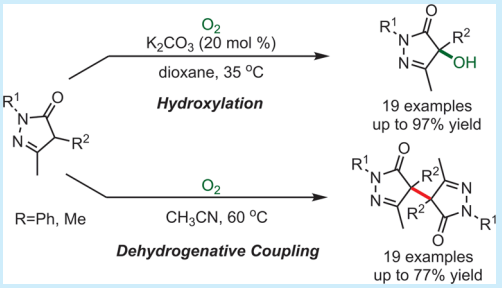
Xuguang Sheng,[†,‡] Jinlong Zhang,[†] Huameng Yang,[†] and Gaoxi Jiang*[,†]

[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: A practical and tunable transition-metal-free aerobic oxidation of pyrazol-5-ones preparing either 4-hydroxypyrazoles (via C−H hydroxylation) or bispyrazoles (via dehydrogenative homocoupling) is described. The K_2CO_3/dioxane reagent system predominately promoted hydroxylation to deliver the α-hydroxylated pyrazoles. In contrast, the formation of bispyrazoles was overwhelmingly preferred with CH_3CN as the reaction medium without any additives.



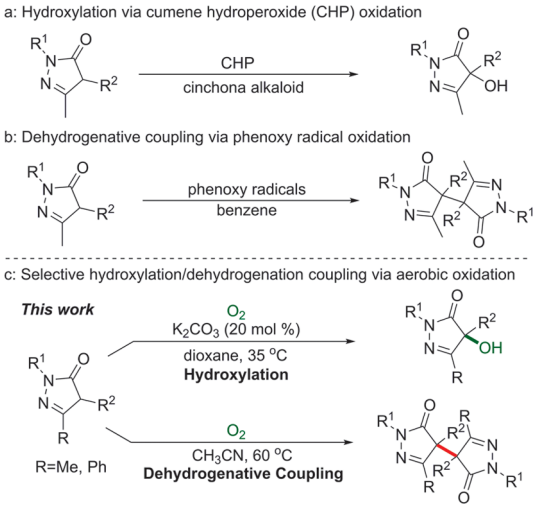
Molecular oxygen is an essential part of multicellular life on Earth and plays a significant role in biological metabolism.[1] Biological metalloenzymes that frequently contain catalytic metal centers usually utilize molecular oxygen as an oxidant to oxidize a variety of substrates, namely, oxygenase and oxidase.[2] The biomimetic approaches employing abundant, nontoxic, and environmentally benign molecular oxygen as an oxygen atom source or oxidant into various organic reactions have potential in the development of green and sustainable chemistry.[3] As two important transformations in this field, oxidative C−H hydroxylation[4] and C−C coupling reaction[3,5] have attracted considerable attention for the synthesis of important biological and pharmaceutical molecules. A traditional method for access to C−H hydroxylation is the direct use of organic oxidants (i.e., DMD,[6a−c] oxaziridines,[6d,e] *m*-CPBA,[6f] ROOH,[6g,h] H_2O_2[6i]) or with O_2 by transition-metal catalysis (i.e., Pd,[7a,b] Ce,[7c−e] Co,[7f] Mn[7g,h]). From an atom-economical and ecological point of view, the requirement for stoichiometric amounts of organic oxidants or heavy metals presents a host of disadvantages. Afterward, transition-metal-free aerobic oxidative C−H hydroxylation by organo-,[8] phase transfer,[9] or inorganic salt[10] catalysis was realized. Despite those remarkable advances, the use of $P(OEt)_3$ for reduction of superoxide intermediate to a final alcohol product is necessary in most cases, which inevitably produces waste.[9d,f,g,10a,b] On the other hand, the oxidative homocoupling of α-tertiary carbon adjacent to a carbonyl function group could be an efficient tool for C−C bond formation. Accordingly, a wide range of catalytic processes have been developed using metal oxidants (i.e., $KMnO_4$, V_2O_5, $FeCl_2$)[11] or organic oxidants (i.e., CAN and I_2),[12] and only a few examples of aerobic oxidative homocoupling catalyzed by CuCl[13a] and Cu_2O[13b] were reported. Nevertheless, further excavation of aerobic homocoupling of carbonyl compounds under mild conditions, particularly without additives, is in great demand yet remains challenging.

Pyrazol-5-one skeletons represent privileged structural units ubiquitously appearing in biologically active natural products and synthetic drugs,[14] such as the first synthetic antipyretic and analgesic drug by Ludwig Knorr in 1883,[14c,d] antibacterial agents,[14e] and p38 inhibitors.[14f] Concerning extensive applications of multifunctionalized pyrazol-5-ones[15,16] and our sustaining interest in the aerobic oxidative reactions,[17] we determined to devote our efforts on the exploration for efficient derivatization of pyrazoles by an aerobic oxidative strategy. Recently, Wang and co-workers reported an oxidative hydroxylation at the C4-position of pyrazol-5-ones with cumene hydroperoxide (CHP) as the oxidant (Scheme 1a).[18] In 1993, the homocoupling of pyrazol-5-ones was first demonstrated by Meske's group using phenoxy radicals as oxidants (Scheme 2b).[19] To the best of our knowledge, the direct aerobic oxidation of pyrazol-5-ones for both hydroxylation and homocoupling is unprecedented and still remains a great challenge. Herein, we present the first switchable aerobic oxidation of pyrazol-5-ones to afford either 4-hydroxypyrazoles (via C−H hydroxylation) or bispyrazoles (via C−C homocoupling). The K_2CO_3/dioxane system predominately promoted the aerobic hydroxylation; by contrast, the aerobic homocoupling was overwhelmingly preferred when CH_3CN was used as the solvent without any additives (Scheme 1c). Moreover, these two kinds of reactions proceeded smoothly in air, making this tunable aerobic oxidation more attractive.

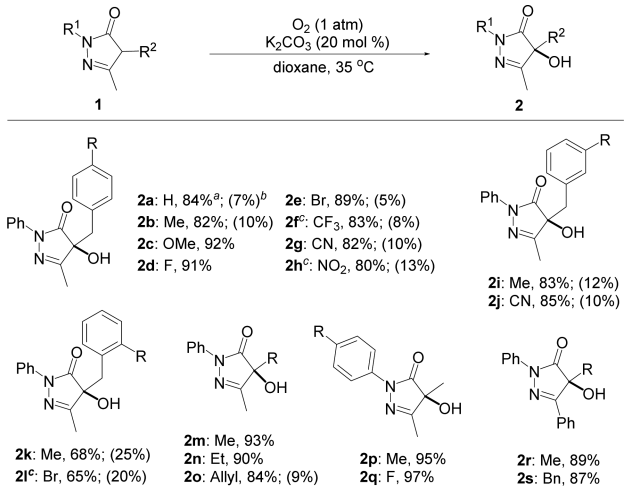
Received: March 30, 2017

DOI: 10.1021/acs.orglett.7b00951
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Oxidative Hydroxylation/Homocoupling of Pyrazol-5-ones



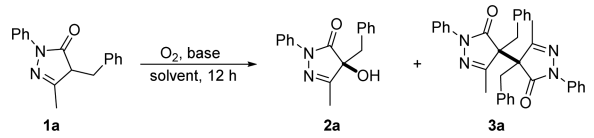
Scheme 2. Scope of Aerobic Oxidative Hydroxylation*



*Reaction conditions: pyrazol-5-ones **1** (0.2 mmol), K_2CO_3 (20 mol %), dioxane (3.0 mL), O_2 (1 atm), 35 °C, 12 h. [a]Yield of isolated product. [b]Yield of isolated corresponding homocoupling product is in parentheses. [c]Reaction was conducted in DMSO (3.0 mL) due to insolubility of substrate in dioxane.

Initially, pyrazol-5-one **1a** was chosen as the model substrate to optimize reaction conditions of this unprecedented oxidation at 60 °C for 12 h. As shown in Table 1, the reaction occurred readily to give a mixture of products, and relatively high yields of 43 and 73% were obtained for **2a** and **3a** in dioxane and CH_3CN, respectively (entries 1–7). Next, various organic and inorganic bases were used in dioxane to only improve the selectivity of product **2a**, and the results showed that K_2CO_3 was superior to provide **2a** in a yield of 84% (entries 8–13). Screening of the reaction temperature indicated that the best outcomes were acquired at 35 °C in terms of reaction time and product yield (entries 14–16). If the base loading was increased from 20 to 40 mol %, no obvious influence on the reaction results was detected, whereas a lower yield of 79% was obtained with a decreased base loading to 10 mol % (entries 17 and 18) (for solvent screening, see Supporting Information). Complementarily and competitively with the above hydroxylation process, we commenced investigating the homocoupling of pyrazol-5-one **1a** in CH_3CN

Table 1. Optimization of the Reaction Conditions for Aerobic Oxidation of Pyrazoles[a]



entry	solvent	base (mol %)	temp (°C)	**2a**/**3a** yield (%)[b]
1	CH_2Cl_2		60	21/35
2	toluene		60	38/51
3	THF		60	39/49
4	CH_3CN		60	19/73
5	dioxane		60	43/50
6	DMSO		60	41/48
7	DMF		60	36/51
8	dioxane	K_2CO_3 (20)	60	84/8
9	dioxane	Na_2CO_3 (20)	60	81/10
10	dioxane	NaOAc (20)	60	77/16
11	dioxane	K_2PO_4 (20)	60	82/11
12	dioxane	Et_3N (20)	60	75/13
13	dioxane	DBU (20)	60	78/15
14	dioxane	K_2CO_3 (20)	80	80/13
15	dioxane	K_2CO_3 (20)	35	84/8
16[c]	dioxane	K_2CO_3 (20)	20	85/9
17	dioxane	K_2CO_3 (40)	35	83/8
18	dioxane	K_2CO_3 (10)	35	79/15
19[d,e]	dioxane	K_2CO_3 (20)	35	78/9
20	CH_3CN		80	23/69
21[e]	CH_3CN		35	12/71
22[d]	CH_3CN		60	17/65

[a]Reaction conditions: **1a** (0.2 mmol) was stirred in solvent (3.0 mL) under O_2 (1 atm) with or without base for 12 h. [b]Yield of isolated product. [c]Reaction for 20 h. [d]In air (1 atm). [e]Reaction for 40 h.

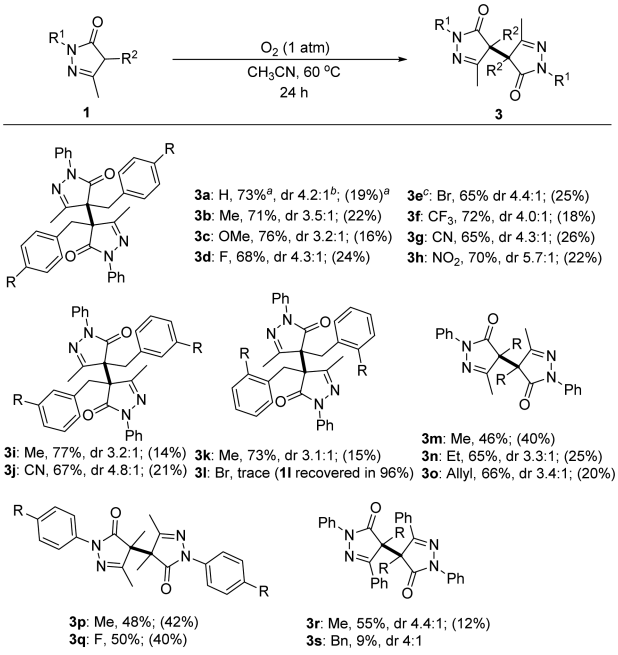
and found that the oxidative homocoupling preferentially occurred to produce bispyrazole **3a** in a reasonable yield of 73% at 60 °C (entries 4, 20, and 21). Excitingly, products **2a** and **3a** were also synthesized in 78 and 65% yields in air, although a prolonged reaction time is necessary (entries 19 and 22). It should be noted that the mixture of **2a** and **3a** can be completely separated by one flash column chromatography.

Under the optimized reaction conditions shown in entry 15 of Table 1, we first investigated the substrate scope of the aerobic oxidative hydroxylation (Scheme 2). Substituents at the *para*- or *meta*-position in 4-benzylpyrazoles were very compatible regardless of electric characteristics, leading to the tertiary alcohols **2b–j** in good yields of 80–92%. For substrates bearing a methyl group or bromine atom at the *ortho*-position, the reaction gave rise to the corresponding products **2k** or **2l** in slightly lower yields and selectivity. Significantly, substituents at the C4-position of pyrazol-5-ones can be easily expanded to methyl, ethyl, and allyl groups, and the desired compounds **2m–o** were produced concisely in 84–93% yields. Furthermore, other methyl-substituted pyrazol-5-ones **1p** and **1q** were also applicable reactants to furnish exclusively the hydroxylation products **2p** and **2q** in excellent yields of 95 and 97%, respectively. Remarkably, 3-phenylpyrazoles **1r** and **1s** were successfully reacted to synthesize the corresponding compounds **2r** and **2s** in 89 and 87% yields, respectively.

Subsequently, the same substrates **1a–s** were subjected to the optimal reaction conditions of aerobic oxidative homocoupling shown in entry 4 of Table 1. As depicted in Scheme 3, reactions of

DOI: 10.1021/acs.orglett.7b00951
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Scope of Aerobic Oxidative Homocoupling*



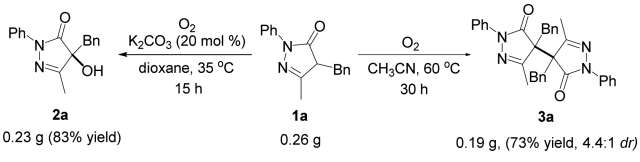
*Reaction conditions: pyrazol-5-ones **1** (0.2 mmol), CH_3CN (3 mL), O_2 (1 atm), 60 °C, 24 h. [a]Yield of isolated product, the yield of isolated corresponding hydroxylation product is in parentheses. [b]The dr value was determined by ^1H NMR. [c]Reaction for 4 days.

different 4-benzylpyrazoles **1a–k** proceeded smoothly to furnish the coupling products bispyrazoles **3a–k** in 65–77% yields and up to 5.1:1 dr with reasonable selectivity in the above competitive hydroxylation process. Only trace transformation occurred with **1l**, and 96% of substrate was recovered. Moreover, with treatment of the starting materials **1m–o** in this transformation, compounds **3m–o** were obtained in 46–66% yields. In the case of 4-methylpyrazol-5-one **1m**, only one diastereomer was identified by ^1H NMR spectroscopy. Also, other methyl-substituted molecules **1p** and **1q** were tolerated to afford products **3p** and **3q** in yields of 48 and 50%, respectively. When 3-phenylpyrazole **1r** was used as reaction substrate, a 55% yield and 4.4:1 dr were detected for product **3r**. However, a poor yield of 9% was obtained for **3s**, likely because of the high steric hindrance between two benzyl groups in product **3s**.

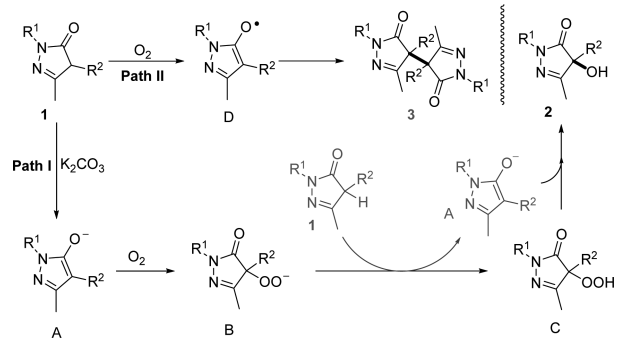
For practicality of this transformation to be highlighted, both hydroxylation and homocoupling reactions of substrate **1a** were conducted under the optimized reaction conditions in 1 mmol scale (Scheme 4). Gratifyingly, the same high yields of 83 and 73% were acquired for the desired compounds **2a** and **3a**, respectively.

On the basis of these preliminary results and pioneering works on aerobic oxidation of the α-position of C–H in carbonyl compounds, a possible mechanism is proposed in Scheme 5. In

Scheme 4. Synthesis of Both Hydroxylation and Homocoupling Products from 1 mmol Scale of 1a



Scheme 5. Proposed Reaction Mechanism



the presence of molecular oxygen with addition of base (Path I), 4-hydroxylation of pyrazole is preferential due to the fast deprotonation by K_2CO_3, providing the corresponding carbanion **A**, which reacts with O_2 to generate a superoxide anion **B**. Then, a proton migration occurs to form the superoxide **C** and immediately regenerates carbanion **A** that was directly oxidized by O_2 or superoxide **C**. After a failure to separately synthesize the intermediate **C**, we utilized the ^1H NMR spectrum of the reaction mixture to detect the acidic H atom of the superoxide part, and the desired peak was not found. Reasonably, the later redox reaction between carbanion **A** and superoxide **C** occurred faster than O_2, providing the desired 4-hydroxylated product **2**.[9e] Additionally, in the absence of base (path II), the homocoupling predominates. Pyrazole might be auto-oxidized to radical intermediate **D** that undergoes a homocoupling process to deliver bispyrazole products **3**.[13a,b,19]

In conclusion, we have described a practical and tunable aerobic oxidation of pyrazoles from hydroxylation to homocoupling by changing solvent and base under transition-metal-free reaction conditions. The aerobic oxidative hydroxylation was favored in the K_2CO_3/dioxane reagent system to produce a variety of 4-hydroxypyrazoles in high to excellent yields. Complementarily, the aerobic oxidative homocoupling reaction predominately occurred when the reaction was performed in a nitrile solvent without any additives, providing bispyrazoles in good yields. Importantly, the concise synthesis of these two kinds of desired products via automatic oxidation in air with acceptable yields makes this switchable aerobic oxidation more attractive.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00951.

^1H and ^{13}C NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gxjiang@licp.cas.cn. Fax: (+86) 931-4968129.

ORCID

Gaoxi Jiang: 0000-0003-1555-1107

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Hundred Talent Program of Chinese Academy of Sciences (CAS), the National Natural Science

DOI: 10.1021/acs.orglett.7b00951
Org. Lett. XXXX, XXX, XXX–XXX

Foundation of China (21602231), and the Natural Science Foundation of Jiangsu Province (Grant Nos. BK20151235 and BK20160396) is gratefully acknowledged.

REFERENCES

(1) (a) Holland, H. D. *The Chemistry of the Atmosphere and Oceans*; Wiley: New York, 1978. (b) Levine, J. S.; Augustsson, T. R.; Natarajan, M. *Origins Life* **1982**, *12*, 245.

(2) (a) Snyder, R. A.; Butch, S. E.; Reig, A. J.; DeGrado, W. F.; Solomon, E. I. *J. Am. Chem. Soc.* **2015**, *137*, 9302. (b) Brown-Marshall, C. D.; Diebold, A. R.; Solomon, E. I. *Biochemistry* **2010**, *49*, 1176. (c) Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 12232.

(3) For reviews, see: (a) Elwell, C. E.; Gagnon, N. L.; Neisen, B. D.; Dhar, D.; Spaeth, A. D.; Yee, G. M.; Tolman, W. B. *Chem. Rev.* **2017**, *117*, 2059. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (d) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736. (e) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (f) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (g) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088. (h) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506. (i) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (j) Stahl, S. S. *Science* **2005**, *309*, 1824. (k) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (l) Schweitzer, C.; Schmidt, R. *Chem. Rev.* **2003**, *103*, 1685. (m) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.

(4) For a review, see: Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637.

(5) For reviews, see: (a) Varun, B. V.; Dhineshkumar, J.; Bettadapur, K. R.; Siddaraju, Y.; Alagiri, K.; Prabhu, K. R. *Tetrahedron Lett.* **2017**, *58*, 803. (b) Girard, S. A.; Knauber, T.; Li, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (c) Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014**, *47*, 3459. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(6) For examples using DMD, see: (a) Adam, W.; Smerz, A. K. *Tetrahedron* **1996**, *52*, 5799. (b) Smith, A. M.; Rzepa, H. S.; White, A. J.; Billen, D.; Hii, K. K. *J. Org. Chem.* **2010**, *75*, 3085. (c) Smith, A. M.; Billen, D.; Hii, K. K. M. *Chem. Commun.* **2009**, 3925. Using oxaziridines: (d) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (e) Davis, F. A.; Liu, H.; Chen, B.-C.; Zhou, P. *Tetrahedron* **1998**, *54*, 10481. Using *m*-CPBA: (f) Andriamialisoa, R.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1985**, *26*, 3563. Using ROOH: (g) Acocella, M. R.; Mancheño, O. G.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2004**, *69*, 8165. (h) Lian, M.; Li, Z.; Du, J.; Meng, Q.; Gao, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 6525. Using H_2O_2: (i) Li, D. M.; Schroder, K.; Bitterlich, B.; Tse, M. K.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5976. Using other oxidants: (j) Vedejs, E.; Engler, D.; Telschow, J. *J. Org. Chem.* **1978**, *43*, 188. (k) Schultz, A. G.; Holoboski, M. A. *Tetrahedron Lett.* **1993**, *34*, 3021. (l) Duschek, A.; Kirsch, S. F. *Chem. - Eur. J.* **2009**, *15*, 10713. (m) Yu, J.; Cui, J. A.; Zhang, C. *Eur. J. Org. Chem.* **2010**, *2010*, 7020. (n) Tsang, A. S.-K.; Kapat, A.; Schoenebeck, F. *J. Am. Chem. Soc.* **2016**, *138*, 518.

(7) For examples using Pd, see: (a) Monguchi, Y.; Takahashi, T.; Iida, Y.; Fujiwara, Y.; Inagaki, Y.; Maegawa, T.; Sajiki, H. *Synlett* **2008**, *2008*, 2291. (b) Chuang, G. J.; Wang, W. K.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760. Using Ce: (c) Christoffers, J.; Werner, T. *Synlett* **2002**, *2002*, 119. (d) Christoffers, J.; Werner, T.; Unger, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, *2003*, 425. (e) Christoffers, J.; Kauf, T.; Werner, T.; Rossle, M. *Eur. J. Org. Chem.* **2006**, *2006*, 2601. (f) Rossle, M.; Christoffers, J. *Tetrahedron* **2009**, *65*, 10941. Using Co: (g) Baucherel, X.; Levoirier, E.; Uziel, J.; Juge, S. *Tetrahedron Lett.* **2000**, *41*, 1385. Using Mn: (h) Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668. (i) Lamarque, L.; Méou, A.; Brun, P. *Can. J. Chem.* **2000**, *78*, 128. Using other transition metals: (j) Watanabe, T.; Ishikawa, T. *Tetrahedron Lett.* **1999**, *40*, 7795.

(8) (a) Miao, C.-B.; Wang, Y.-H.; Xing, M.-L.; Lu, X.-W.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2013**, *78*, 11584. (b) Buckley, B. R.; Fernández, D.-R. B. *Tetrahedron Lett.* **2013**, *54*, 843. (c) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914. (d) Sundén, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.

(9) (a) Zhou, S.; Zhang, L.; Li, C.; Mao, Y.; Wang, J.; Zhao, P.; Tang, L.; Yang, Y. *Catal. Commun.* **2016**, *82*, 29. (b) Wang, Y.; Yin, H.; Tang, X.; Wu, Y.; Meng, Q.; Gao, Z. *J. Org. Chem.* **2016**, *81*, 7042. (c) Wang, Y.; Zheng, Z.; Lian, M.; Yin, H.; Zhao, J.; Meng, Q.; Gao, Z. *Green Chem.* **2016**, *18*, 5493. (d) Sim, S.-B. D.; Wang, M.; Zhao, Y. *ACS Catal.* **2015**, *5*, 3609. (e) Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* **2012**, *14*, 4762. (f) Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. *Org. Lett.* **2010**, *12*, 1496. (g) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.

(10) (a) Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548. (b) de Vries, E. F. J.; Ploeg, L.; Colao, M.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1123.

(11) (a) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408. (d) Kise, N.; Tokioka, K.; Aoyama, Y.; Matsumura, Y. *J. Org. Chem.* **1995**, *60*, 1100. (e) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (f) Tokuda, M.; Shigei, T.; Itoh, M. *Chem. Lett.* **1975**, *4*, 621. (g) Kato, H.; Tani, K.; Kurumisawa, H.; Tamura, Y. *Heterocycles* **1987**, *26*, 1313. (h) Andersen, K. K.; Bray, D. D.; Kjær, A.; Lin, Y.; Shoja, M.; Dooryhee, E. *Acta Chem. Scand.* **1997**, *51*, 1000.

(12) (a) Ghosh, S.; Chaudhuri, S.; Bisai, A. *Org. Lett.* **2015**, *17*, 1373. (b) Nicolaou, K. C.; Gray, D. J. *J. Am. Chem. Soc.* **2004**, *126*, 607. (c) Nicolaou, K. C.; Gray, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 761.

(13) (a) Kozlowski, M. C.; DiVirgilio, E. S.; Malolanarasimhan, K.; Mulrooney, C. A. *Tetrahedron: Asymmetry* **2005**, *16*, 3599. (b) Fang, X.; Zhang, K.; Yao, H.; Huang, Y. *Org. Biomol. Chem.* **2016**, *14*, 8030.

(14) (a) Varvounis, G. Pyrazol-3-ones. Part IV: Synthesis and Applications. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed.; Academic Press: New York, 2009; Vol. *98*, p 143. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Tainter, M. L.; Ann, N. Y. *Ann. N. Y. Acad. Sci.* **1948**, *51*, 3. (d) Brune, K. *Acute Pain* **1997**, *1*, 33. (e) *Dipyrone. Martindale: The Complete Drug Reference*; Brayfield, A., Ed.; Pharmaceutical Press: London, 2014. (f) Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; VanRens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; Brown, K. K.; Juergens, K.; Taiwo, Y. O.; Janusz, M. J. *J. Med. Chem.* **2004**, *47*, 2724.

(15) For a review of pyrazol-3-one derivatization, see: (a) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890. For several recent examples, see: (b) Zhu, Z.-Q.; Shen, Y.; Liu, J.-X.; Tao, J.-Y.; Shi, F. *Org. Lett.* **2017**, *19*, 1542. (c) Lin, H.-C.; Wang, P.-S.; Tao, Z.-L.; Chen, Y.-G.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2016**, *138*, 14354. (d) Amr, F. I.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2016**, *358*, 1583.

(16) For our recent work on derivatization of pyrazoles, see: Zhou, H.; Wei, Z.; Zhang, J.; Yang, H.; Xia, C.; Jiang, G. *Angew. Chem., Int. Ed.* **2017**, *56*, 1077.

(17) (a) Li, J.; Zhang, J.; Yang, H.; Gao, Z.; Jiang, G. *J. Org. Chem.* **2017**, *82*, 765. (b) Li, J.; Zhang, J.; Yang, H.; Jiang, G. *J. Org. Chem.* **2017**, *82*, 3284.

(18) (a) Xue, F.; Bao, X.; Zou, L.; Qu, J.; Wang, B. *Adv. Synth. Catal.* **2016**, *358*, 3971. (b) Guthrie, D. A.; Ho, A.; Takahashi, C. G.; Collins, A.; Morris, M.; Toscano, J. P. *J. Org. Chem.* **2015**, *80*, 1338.

(19) Schulz, M.; Meske, M. *J. Prakt. Chem./Chem.-Ztg.* **1993**, *335*, 607.

DOI: 10.1021/acs.orglett.7b00951
Org. Lett. XXXX, XXX, XXX−XXX