Organic LETTERS

Letter

pubs.acs.org/OrgLett

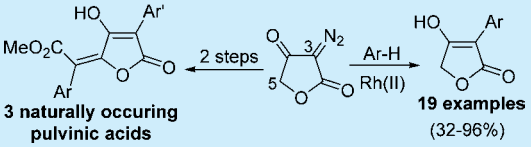
Catalytic Undirected Intermolecular C−H Functionalization of Arenes with 3-Diazofuran-2,4-dione: Synthesis of 3-Aryl Tetronic Acids, Vulpinic Acid, Pinastric Acid, and Methyl Isoxerocomate

Amarender Manchoju and Sunil V. Pansare*

Department of Chemistry, Memorial University, St. John's, Newfoundland, Canada, A1B 3X7

Supporting Information

ABSTRACT: A variety of 3-aryl tetronic acids have been synthesized by an undirected, intermolecular C−H functionalization of arenes with 3-diazofuran-2,4-dione. This methodology featured as a key step in the synthesis of a series of naturally occurring 3-aryl-5-arylidene tetronic acids (pulvinates) from commercially available tetronic acid. Salient features of the pulvinic acid synthesis include a one-step, stereoselective synthesis of the C5 arylidene group and a single step introduction of the C3 aryl substituent.



Tetronic acid (4-hydroxy-2-5[H]-furanone) functionality has attracted considerable attention in recent years as a distinctive feature of many natural products.[1] Many tetronic acid derivatives display a wealth of biological activities which include insecticidal and acaricidal,[2] HIV−I protease inhibitory,[3] antineoplastic,[4] antiinflammatory,[5] and cyclooxygenase inhibitory activity.[6] In addition, these tetronic acids are also of interest for their role as pigments in mushrooms and lichens.[1] Among a large group of structurally related tetronates that are substituted at C3 with an aryl group are pulvinic acid (**1**, Figure 1), vulpinic acid (**2**), 4-hydroxypulvinic acid (**3**), pinastric acid (**4**), and their oxygenated analogues[7] such as xerocomic acid (**5**), methyl isoxerocomate (**6**), and variegatic acid (**7**). More elaborate congeners include xerocomorubin (**8**),[8a] norbadione A (**9**),[8b] and badione A (**10**).[8b]

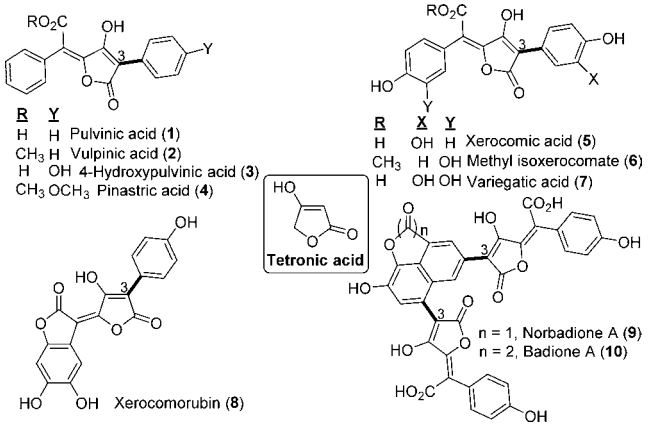
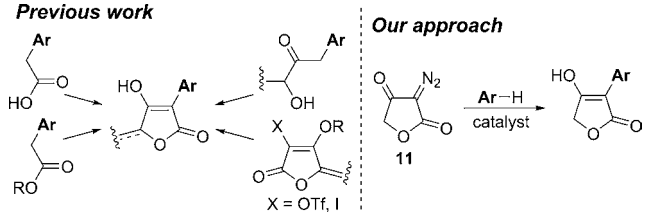


Figure 1. Naturally occurring 3-aryl tetronic acid derivatives.

Synthetic analogs of pulvinic acid have also shown antioxidant,[9a] antiulcer,[9b] and radioprotective[9c] properties whereas the natural pulvinate, variegatic acid (**7**, Figure 1), is of interest as a precursor of stable, natural blue-colorant for foods and beverages.[9d] The synthesis of tetronic acids has therefore been extensively investigated in recent years.[10]

Practically all of the reported syntheses of 3-aryl tetronates require a starting material which contains the aryl group that is required in the target. The majority of these methods use aryl acetic acids,[11] esters,[12] or α-hydroxy alkyl aryl ketones[13] as the starting materials (Scheme 1). An alternative, but synthetically intensive, approach[14] involves the cross-coupling of aryl boronic acid derivatives with C3-functionalized tetronic acid derivatives. All of these procedures are primarily limited by the availability of suitably functionalized starting materials, and methodology that overcomes this limitation would be useful.

Scheme 1. Strategies for the Synthesis of 3-Aryl Tetronic Acids



With this objective in mind, a review of the literature indicated a scarcity of reports on the synthetic applications of 3-diazofuran-2,4-dione (**11**, Scheme 1)[15] and only a sole report describing an undesired, low yield, C−H insertion reaction.[15c] We were therefore intrigued by the prospect of developing intermolecular aryl C−H insertion reactions of **11**, easily prepared from commercially available tetronic acid in one step,[15a,c] as a direct route to 3-aryl tetronates (Scheme 1). Herein, we describe preliminary results on this approach and an

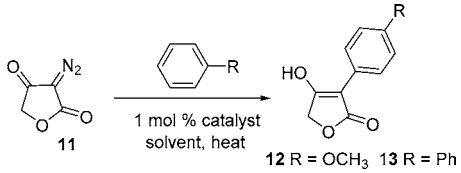
Received: October 13, 2016
Published: November 8, 2016

DOI: 10.1021/acs.orglett.6b03087
Org. Lett. 2016, 18, 5952−5955

application of the methodology in the synthesis of vulpinic acid (**2**), pinastric acid (**4**), and methyl isoxerocomate (**6**, Figure 1).

Intramolecular and substrate-directed C−H functionalization of arenes with diazo compounds is well-known.[16] Undirected, intermolecular, arene C−H functionalization reactions[17a] have also been investigated. The majority of these studies have examined α-aryl-α-diazoacetates[17b−i] or 3-diazooxindoles,[17j−l] and only a few arene C−H functionalization studies are reported with 2-diazo-1,3-dicarbonyl compounds.[17m−q] Given the relative shortage of information available on the key step of our proposed synthetic plan, a survey of catalysts and reaction conditions was necessary. Accordingly, we first attempted the reaction of **11** with anisole in the presence of $Cu(OTf)_2$,[17p] $Co(OAc)_2$,[18] and $(Ph_3P)_3AuCl/AgSbF_6$[17c] as catalysts. With $Cu(OTf)_2$, **12** was obtained in low yield (11%, Table 1, entry 1). Although the Co and Au derived catalysts are known to promote diazo decomposition, only unreacted **11** was observed in these reactions.

Table 1. Optimization of the Intermolecular Aryl C−H Insertion Reaction of 11



entry	catalyst	solvent	t (h)	prod	yield (%)
1	$Cu(OTf)_2$	–		**12**	11 (36)[a]
2	$Co(OAc)_2$	–		–	–
3	$AuCl/AgSbF_6$	–		–	–
4	$Rh_2(OAc)_4$	–		**12**	96
5	$Rh_2(OAc)_4$	$(CH_2)_2Cl_2$[b]	12	**13**	36
6		CH_2Cl_2[b]	79		21 (34)[a]
7		$PhCF_3$[c]	168		47 (55)[a]
8		[bmim]PF_6[b]	65		13
9		[bmim]BF_4[b]	96		16 (22)[a]
10	$Rh_2(CF_3CO_2)_4$	$(CH_2)_2Cl_2$	24		27
11		CH_2Cl_2	96		–
12		$PhCF_3$[d]	5		51 (67)[e]
13		$PhCF_3$[d]	21		35(46)[e,f]
14		[bmim]PF_6	92		19 (22)[a]
15		[bmim]BF_4	72		42
16	$Rh_2(NHCOC_3F_7)_4$	$(CH_2)_2Cl_2$	5		19
17		CH_2Cl_2	7		–
18		$PhCF_3$[g]	2.5		23
19		[bmim]PF_6	22		21
20		[bmim]BF_4	55		23

[a]Based on recovered **11**. [b]At reflux or at 100 °C for ionic liquids. [c]At 70 °C. [d]At 100 °C. [e]Including regioisomer. [f]Reaction with 2 equiv of biphenyl. [g]Reaction at 80 °C.

We therefore turned to the more conventional rhodium-based catalysts. Interestingly, heating a solution of **11** in anisole in the presence of $Rh_2(OAc)_4$ provided **12** in excellent yield (96%) as a single regioisomer (Table 1, entry 4). This procedure (Method A) was suitable for simple arenes which could be used as the solvent and then easily separated from the tetronic acid product and recovered.

In order to expand the scope of the methodology to other arenes, an optimization of the insertion reaction was conducted by varying the solvent, catalyst, and stoichiometry of the arene. These studies, with biphenyl as the representative arene, are summarized in Table 1.

Conventional chlorinated solvents, ionic liquids, and α,α,α-trifluoromethylbenzene were selected as the reaction medium, and a set of rhodium(II) catalysts differing in the ligand were screened. The choice of rhodium catalysts that are more electrophilic than $Rh_2(OAc)_4$ was based on previous studies on competitive intramolecular reactions of diazo carbonyl compounds[19] in which electron-deficient rhodium catalysts favored aromatic substitution (net C−H insertion) reactions over competing cyclopropanation. As seen from Table 1, almost all of the reactions provided **13**, but α,α,α-trifluoromethylbenzene was clearly a superior solvent (Table 1, entries 7 and 12), and $Rh_2(CF_3CO_2)_4$ was the catalyst of choice (compare entries 7, 12, and 18 in Table 1). The best results were obtained with an excess of biphenyl (4 equiv, entry 12), and reducing this amount was not beneficial (46% yield with 2 equiv of biphenyl; Table 1, entry 13). This procedure ($PhCF_3$ as the solvent, $Rh_2(CF_3CO_2)_4$ as the catalyst, and 4 equiv of the arene; Method B) or Method A, described above, were applicable to the C−H insertion reactions of **11** with a variety of arenes to provide **12**−**31** (Figure 2).

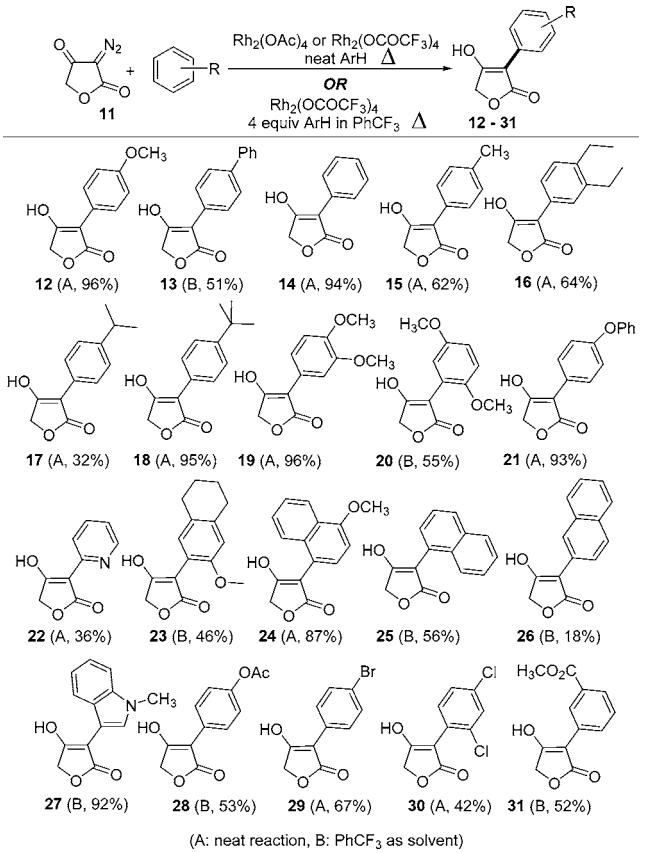


Figure 2. Intermolecular aryl C−H insertion reactions of **11**.

The C−H insertion reactions of **11** with alkyl benzenes and with electronically activated arenes proceeded readily and in moderate to good yield (method A, 12 examples, 72% average yield; method B, 7 examples, 60% average yield). Interestingly, **11** also reacted with methyl benzoate to provide **31** (52%), but reactions with more electron-deficient arenes such as nitrobenzene, acetophenone, and benzonitrile were unsuccessful. The regiochemistry of C−H functionalization is what would be

DOI: 10.1021/acs.orglett.6b03087
Org. Lett. 2016, 18, 5952−5955

expected for electrophilic aromatic substitution of the arene,[20] and in a few cases, regioisomeric products were obtained (**13**, *p*/*o* = 3.1:1; **25**/**26** = 3.1:1; **29**, *p*/*o* = 3.5:1) which were easily separated. The results suggest that the carbenoid derived from **11** reacts with the arenes as an electrophile. This reactivity is consistent with the superior performance of $Rh_2(OCOCF_3)_4$ which presumably increases the electrophilicity of the bound carbene.[19]

Having established a general procedure for preparing 3-aryl tetronic acid derivatives, we next examined the application of our method in the synthesis of selected, naturally occurring pulvinic acids (Figure 1). While the conversion of 3-aryl tetronic acids to pulvinates is well-known,[14a,21] our objective was to develop a modular functionalization of **11** by first introducing the arylidene functionality at C5 (Figure 3) and

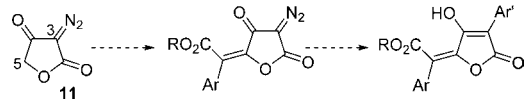


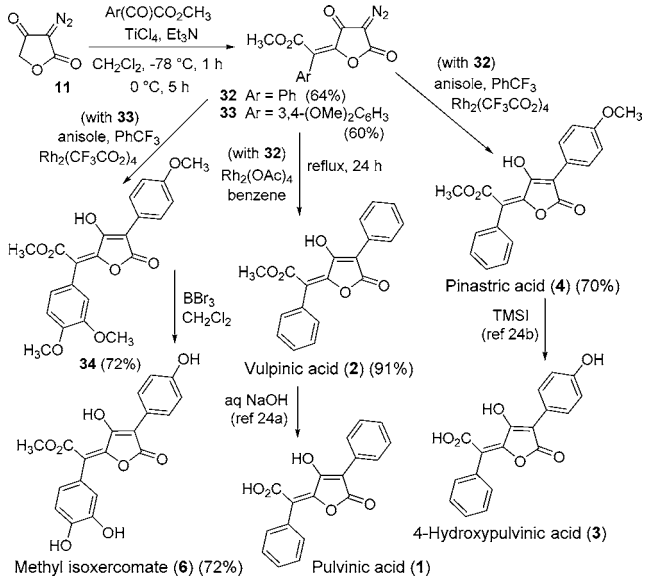
Figure 3. Strategy for the synthesis of naturally occurring pulvinates from **11**.

then adding the C3 aryl group employing the C−H insertion procedure. Compared to current methods for pulvinic acid synthesis, our procedure would use **11** as the common starting material for all of the structurally related tetronate natural products (Figure 3).

Previous syntheses of C5-arylidene tetronic acid derivatives from 3-aryl tetronic acids have relied on protocols that involve multistep assembly of the tetronate ring[14a,21a,b] or Wittig reaction of a preformed C3-substituted tetronate derivative.[11a] More recent strategies also involve several steps, specifically: (a) an aldol reaction of a C3 substituted tetronic acid derivative with a α-keto ester; (b) dehydration of the aldol product by mesylation and elimination,[21b] or by conversion to the trifluoroacetate and elimination; and (c) photoisomerization of the mixture of isomeric alkenes so obtained to the naturally occurring *E*-isomer.[21a,b] Stereoisomers of the required alkene products are also obtained in the earlier procedures.[11a,14a,21a] Clearly, an alternative to these multistep procedures, and especially to the stereorandom synthesis of the arylidene portion, would be useful.

Our search for alternative procedures focused on the possibility of using a mild aldolization protocol that would not affect the diazo group in **11**. Initial attempts with **11** and methyl benzoylformate in the presence of $MgBr_2$ and triethylamine[22a] provided a very low yield of the required aldol product. However, the use of a stronger Lewis acid ($TiCl_4$, Et_3N, −78 °C)[22b] provided a mixture of the aldol product and the dehydration product **32** (Scheme 2). A brief optimization revealed that warming the reaction mixture (0 °C) provided only **32** (64%, Scheme 2) with excellent diastereoselectivity (*E*/*Z* = ∼40:1).[23] Similarly, **33** was also obtained as a single isomer (60%) using this procedure. With **32** and **33** in hand, their C−H insertion reactions were examined. Gratifyingly, Rh(II) catalyzed reactions of **32** with benzene and anisole (4 equiv in $PhCF_3$) provided vulpinic acid (**2**, 91%) and pinastric acid (**4**, 70%) respectively. A similar reaction of **33** with anisole provided **34** (72%) which was treated with BBr_3 to furnish methyl isoxerocomate (**6**, 72%, Scheme 2). The conversion of vulpinic acid and pinastric acid to pulvinic acid (**1**) and 4-hydroxypulvinic acid (**3**) respectively[24a,b] is known.

Scheme 2. Synthesis of Naturally Occurring Tetronic Acid Derivatives



The formation of **2**, **4**, and **6** also confirms the stereochemical assignments for **32** and **33**.

In conclusion, a one-step synthesis of 3-aryl tetronic acids has been developed from 3-diazofuran-2,4-dione. The synthesis of vulpinic acid (**2**), pinastric acid (**4**), and methyl isoxercomate (**6**), as well as a formal synthesis of pulvinic acid (**1**) and 4-hydroxypulvinic acid (**3**), was achieved in three steps from commercially available tetronic acid. To the best of our knowledge, the two-step functionalization of **11** offers the shortest route to these natural products. The methodology provides direct access to a wide range of 3-aryl tetronates and has the advantage of furnishing stereoisomerically pure 5-arylidene tetronates. We anticipate that our modular strategy will be useful for preparing natural product-like libraries of tetronic acid derivatives by systematic variation of the C3 aryl group and the aryl group in the α-keto ester used in the aldol condensation. Current efforts focus on these and other applications of **11**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03087.

Experimental methods and spectroscopic data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: spansare@mun.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

These investigations were supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation.

DOI: 10.1021/acs.orglett.6b03087
Org. Lett. 2016, 18, 5952−5955

REFERENCES

(1) (a) Zaghouani, M.; Nay, B. *Nat. Prod. Rep.* **2016**, *33*, 540. (b) Georgiadis, D. In *Natural Lactones and Lactams*; Janecki, T., Ed.; Wiley: 2014; p 1. (c) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203.

(2) Selected recent reports: (a) Yao, T.-T.; Cheng, J.-L.; Xu, B.-R.; Zhang, M.-Z.; Hu, Y.-Z.; Zhao, J.-H.; Dong, X.-W. *RSC Adv.* **2015**, *5*, 49195. (b) Lamberth, C.; Dinges, J. *Bioactive Heterocyclic Compound Classes*; Wiley-VCH: 2012; p 265. (c) Liu, Z.; Lei, Q.; Li, Y.; Xiong, L.; Song, H.; Wang, Q. *J. Agric. Food Chem.* **2011**, *59*, 12543.

(3) Selected reports: (a) Chrusciel, R.; Strohbach, J. W. *Curr. Top. Med. Chem.* **2004**, *4*, 1097. (b) Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825. (c) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H. B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 136. (d) Yehia, N. A. M.; Antuch, W.; Beck, B.; Hess, S.; Schauer-Vukašinović, V.; Almstetter, M.; Furer, P.; Herdtweck, E.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3121.

(4) Selected reports: (a) Osada, H.; Shimizu, S.; Sodeoka, M.; Hirai, T.; Ishida, K. Jpn. Kokai Tokkyo Koho 2005, JP 2005023048 A 20050127. (b) Shinya, K. PCT Int. Appl. 2003, WO 2003044208 A1 20030530. (c) Lopez, M. D.; Quinoa, E.; Riguera, R. *J. Nat. Prod.* **1994**, *57*, 992.

(5) Foden, F. R.; McCormick, J.; O'Mant, D. M. *J. Med. Chem.* **1975**, *18*, 199.

(6) Duncan, C. J. G.; Cuendet, M.; Fronczek, F. R.; Pezzuto, J. M.; Mehta, R. G.; Hamann, M. T.; Ross, S. A. *J. Nat. Prod.* **2003**, *66*, 103.

(7) Selected reports: (a) Gruber, G.; Kerschensteiner, L.; Steglich, W. *Z. Naturforsch., B: J. Chem. Sci.* **2014**, *69*, 432. (b) Gruber, G.; Kerschensteiner, L.; Marumoto, R.; Steglich, W. *Z. Naturforsch., B: J. Chem. Sci.* **2013**, *68*, 675. (c) van der Sar, S. A.; Blunt, J. W.; Cole, A. L. J.; Din, L. B.; Munro, M. H. G. *J. Nat. Prod.* **2005**, *68*, 1799.

(8) (a) Edwards, R. L.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1529. (b) Steffan, B.; Steglich, W. *Angew. Chem.* **1984**, *96*, 435.

(9) (a) Nadal, B.; Thetiot-Laurent, S. A.-L.; Pin, S.; Renault, J.-P.; Cressier, D.; Rima, G.; Le Roux, A.; Meunier, S.; Wagner, A.; Lion, C.; Le Gall, T. *Bioorg. Med. Chem.* **2010**, *18*, 7931. (b) Wang, X.-D.; Wei, W.; Wang, P.-F.; Yi, L.-C.; Shi, W.-K.; Xie, Y.-X.; Wu, L.-Z.; Tang, N.; Zhu, L.-S.; Peng, J.; Liu, C.; Li, X.-H.; Tang, S.; Xiao, Z.-P.; Zhu, H.-L. *Bioorg. Med. Chem.* **2015**, *23*, 4860. (c) Le Roux, A.; Meunier, S.; Le Gall, T.; Denis, J.-M.; Bischoff, P.; Wagner, A. *ChemMedChem* **2011**, *6*, 561. (d) Newsome, A. G.; Culver, C. A.; van Breemen, R. B. *J. Agric. Food Chem.* **2014**, *62*, 6498.

(10) Selected recent reports: (a) Sophie, A.-L.; Thetiot-Laurent, S. A.-L.; Le Gall, T. *Targets Het. Sys.* **2010**, *14*, 80. (b) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, *2006*, 3157. (c) Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proced. Int.* **2004**, *36*, 33. (d) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181. (e) Yoshii, E.; Takeda, K. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: 1993; p 67. (f) Effenberger, F.; Syed, J. *Tetrahedron: Asymmetry* **1998**, *9*, 817. (g) Athanasellis, G.; Igglessi-Markopoulou, O.; Markopoulos, J. *Bioinorg. Chem. Appl.* **2010**, *2010*, 1.

(11) Selected reports: (a) Haynes, L. J.; Stanners, A. H. *J. Chem. Soc.* **1956**, 4103. (b) Campbell, A. C.; Maidment, M. S.; Pick, J. H.; Stevenson, D. F. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1567. (c) Xiao, Z.-P.; He, X.-B.; Peng, Z.-Y.; Xiong, T.-J.; Peng, J.; Chen, L.-H.; Zhu, H.-L. *Bioorg. Med. Chem.* **2011**, *19*, 1571. (d) Yang, W.; Liu, J.; Zhang, H. *Tetrahedron Lett.* **2010**, *51*, 4874.

(12) Mallinger, A.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2009**, *74*, 1124.

(13) Jerris, P. J.; Wovkulich, P. M.; Smith, A. B., III *Tetrahedron Lett.* **1979**, *20*, 4517.

(14) (a) Ahmed, Z.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3753. (b) Bourdreux, Y.; Nowaczyk, S.; Billaud, C.; Mallinger, A.; Willis, C.; Desage-El Murr, M.; Toupet, L.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2008**, *73*, 22. (c) Willis, C.; Bodio, E.; Bourdreux, Y.; Billaud, C.; Le Gall, T. *Tetrahedron Lett.* **2007**, *48*, 6421.

(15) (a) Studies on O−H bond insertion: Stachel, H. D.; Poschenrieder, H.; Redlin, J.; Schachtner, J.; Zeitler, K. *Liebigs Ann. Chem.* **1994**, 129. Application in heterocycle synthesis: (b) Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Korneev, S. M.; Yufit, D. S. *Org. Biomol. Chem.* **2013**, *11*, 5535. (c) Murphy, P. V.; O'Sullivan, T. J.; Kennedy, B. D.; Geraghty, N. W. A. *J. Chem. Soc. Perkin Trans. 1* **2000**, *13*, 2121.

(16) Selected recent reports: (c) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. - Eur. J.* **2014**, *20*, 17653. (d) Yu, X.-Z.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444. (e) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (f) Ma, B.; Chen, F.-L.; Xu, X.-Y.; Zhang, Y.-N.; Hu, L.-H. *Adv. Synth. Catal.* **2014**, *356*, 416.

(17) (a) Review: Caballero, A.; Díaz-Requejo, M. M.; Fructos, M. R.; Olmos, A.; Urbano, J.; Pérez, P. J. *Dalton Trans.* **2015**, *44*, 20295. (b) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 9817. (c) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (d) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700. (e) Yang, J.-M.; Cai, Y.; Zhu, S.-F.; Zhou, Q.-L. *Org. Biomol. Chem.* **2016**, *14*, 5516. (f) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, 6719. (g) Ma, B.; Wu, Z.; Huang, B.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 9351. (h) Yu, Z.; Qiu, H.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 2257. (i) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 13098. (j) Cao, Z.-Y.; Zhao, Y.-L.; Zhou, J. *Chem. Commun.* **2016**, *52*, 2537. (k) Zhai, C.; Xing, D.; Jing, C.; Zhou, J.; Wang, C.; Wang, D.; Hu, W. *Org. Lett.* **2014**, *16*, 2934. (l) Magar, K. B. S.; Edison, T. N. J. I.; Lee, Y. R. *Org. Biomol. Chem.* **2016**, *14*, 7313. (m) Best, D.; Jean, M.; van de Weghe, P. *J. Org. Chem.* **2016**, *81*, 7760. (n) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112. (o) Rosenfeld, M. J.; Shankar, B. K. R.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2699. (p) Maryanoff, B. *J. Org. Chem.* **1982**, *47*, 3000. (q) Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2624.

(18) Hoffman, R. V.; Shechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 7934.

(19) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.

(20) The structural assignment of **22** and **24** is based on the similarity of the aromatic region resonances in their ^{1}H NMR spectra with those of structurally related compounds. (a) Baraldi, P. G.; Romagnoli, R.; Pavani, M. G.; Nuñez, M.; Tabrizi, M. A.; Shryock, J. C.; Leung, E.; Moorman, A. R.; Uluoglu, C.; Iannotta, V.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2003**, *46*, 794. (b) Korsager, S.; Taaning, R. F.; Skrydstrup, T. *J. Am. Chem. Soc.* **2013**, *135*, 2891.

(21) (a) Ramage, R.; Griffiths, G. J.; Sweeney, J. N. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1547. (b) Gedge, D. R.; Pattenden, G.; Smith, A. G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2127 also see ref 12.

(22) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (b) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415.

(23) Mixtures of *E* and *Z* isomers of **32** were obtained by dehydration of the corresponding aldol product obtained in some of the optimization experiments. The stereochemistry of **32** was assigned as *E* on the basis of a downfield shift of the ester methyl group resonance (δ 3.97) due to anisotropic deshielding by the C4 carbonyl group in *E*-**32** compared to the *Z*-isomer (δ 3.86). For a similar trend in chemical shifts for *E* and *Z* methyl-4-oxo-2-arylpentenoates, see: (a) Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951. (b) Lerche, H.; König, D.; Severin, T. *Chem. Ber.* **1974**, *107*, 1509.

(24) (a) Heurtaux, B.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2005**, *70*, 1474. (b) Pattenden, G.; Pegg, N. A.; Kenyon, R. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2363.

DOI: 10.1021/acs.orglett.6b03087
Org. Lett. 2016, 18, 5952−5955