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Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Chlorides with α-Bromolactones and Related Derivatives

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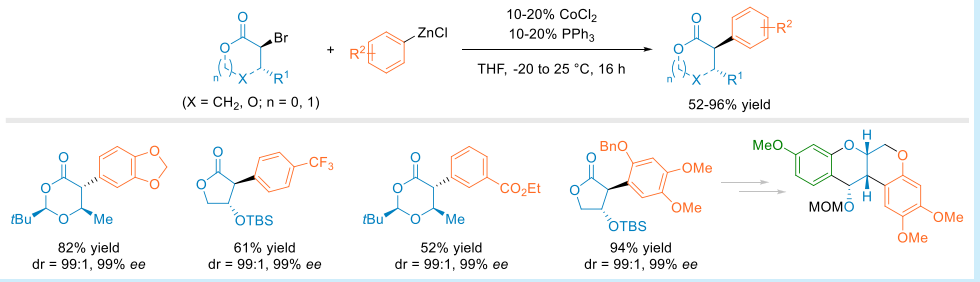
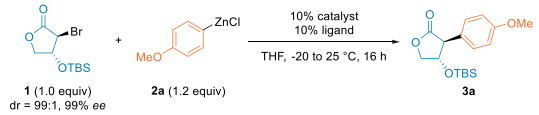


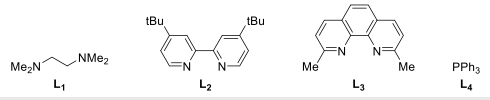
ABSTRACT: α-Bromolactones bearing a substituent in the β-position undergo a highly *trans*-diastereoselective arylation with arylzinc chlorides in the presence of 10−20% $CoCl_2$ and 10−20% PPh_3 in THF under mild conditions (25 °C, 16 h) leading to optically enriched α-arylated lactones and protected aldol products (99% *ee*) in 52−96% yield. The synthetic utility of this arylation was demonstrated by the stereoselective preparation of an artificial rotenoid MOM-protected munduserol derivative.

The preparation of chiral agrochemicals and pharmaceuticals requires general and efficient asymmetric syntheses.[1] Recently, several advances involving Pd- and Ni-catalyzed asymmetric carbon−carbon bond forming reactions have been reported.[2] These transition-metal-catalyzed asymmetric cross-couplings involve expensive[3] or toxic[4] Ni- or Pd-catalysts. Also, reactions involving alkyl-palladium intermediates are often of limited scope due to β-hydrogen elimination side reactions.[5] It was shown that relatively inexpensive and less toxic $CoCl_2$ does efficiently catalyze cross-couplings.[6] Also, organozinc compounds are excellent nucleophilic reagents for various Co-catalyzed cross-coupling reactions, as a broad range of sensitive functional groups are tolerated in these organometallics.[7] 1,2-Substituted alkyl halides were used as electrophiles for *trans*-diastereoselective cobalt-catalyzed cross-coupling reactions.[6h,m,7a,8] In preliminary experiments, the readily available α-bromolactone **1**, which was prepared from D-isoascorbic acid in 99% *ee*,[9] was submitted to an arylation using 4-anisylzinc chloride (**2a**). The formation of product **3a** was optimized using various metallic salts (Table 1). Whereas $CuCl_2$, $CrCl_2$, $MnCl_2$, and $FeCl_2$ were not effective catalysts (entries 1−5), $CoCl_2$ gave excellent results compared to $CoBr_2$ or $Co(acac)_2$ (entries 6−8). The addition of a ligand, such as PPh_3, allowed further yield improvement (entries 9−12). $NiCl_2/PPh_3$ was equally efficient (entry 13).

Table 1. Reaction Conditions Optimization for the Cross-Coupling of *p*-Anisylzinc Chloride (2a) with α-Bromolactone (1)



entry	catalyst	ligand	yield[a]
1	-	-	3%
2	$CuCl_2$	-	-
3	$CrCl_2$	-	4%
4	$MnCl_2$	-	4%
5	$FeCl_2$	-	5%
6	$CoCl_2$	-	86% (83%)[b]
7	$CoBr_2$	-	77%
8	$Co(acac)_2$	-	75%
9	$CoCl_2$	L_1	56%
10	$CoCl_2$	L_2	30%
11	$CoCl_2$	L_3	65%
12	$CoCl_2$	L_4	98% (96%)[c]
13	$NiCl_2$	L_4	98%



[a]Calibrated GC-yield using undecane as internal standard. [b]99.99% $CoCl_2$ was used. [c]Isolated yield of analytically pure **3a** (dr = 99:1, 99% *ee*).

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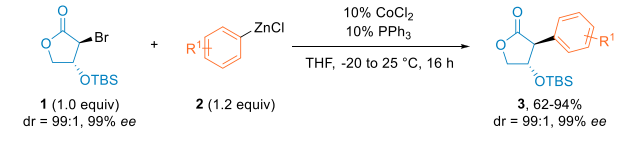
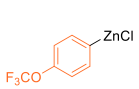
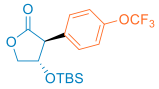
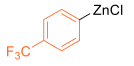
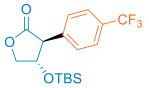
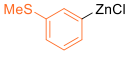
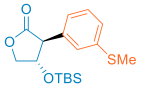
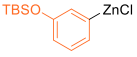
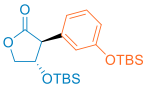
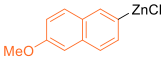
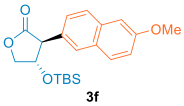
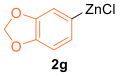
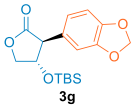
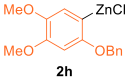
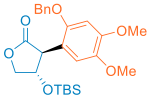
Table 2. Stereoselective Cobalt-Catalyzed Cross-Couplings of Arylzinc Reagents of Type 2 with α-Bromolactone 1



entry	arylzinc reagent	product	yield[a]
1	 **2b**	 **3b**	63%
2	 **2c**	 **3c**	62%
3	 **2d**	 **3d**	63%
4	 **2e**	 **3e**	77%
5	 **2f**	 **3f**	61%
6	 **2g**	 **3g**	84%
7	 **2h**	 **3h**	94%

[a]Isolated yield of analytically pure lactones of type **3**.

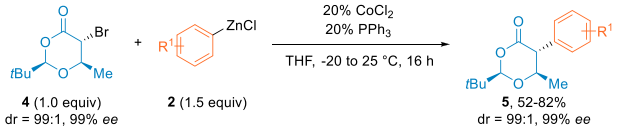
These optimized conditions were then applied to the arylation of α-bromolactone **1** using various arylzinc reagents of type **2** (Table 2).

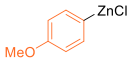
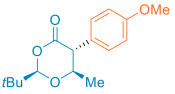
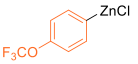
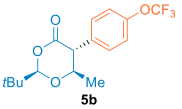
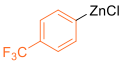
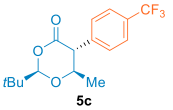
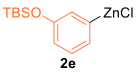
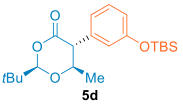
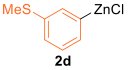
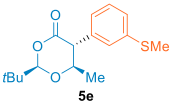
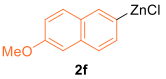
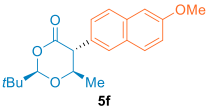
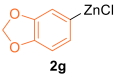
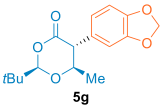
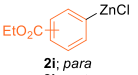
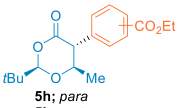
Thus, *p*-trifluoromethoxyphenylzinc chloride (**2b**) was cross-coupled with **1**, leading to the desired α-arylated lactone **3b** in 63% yield (dr = 99:1, 99% *ee*, entry 1). Similarly, the electron-poor organozinc reagent **2c** furnished the 4-trifluorotolyl substituted lactone **3c** in 62% yield (dr = 99:1, 99% *ee*, entry 2). Also, the *meta*-substituted arylzinc reagents **2d** and **2e**, bearing a MeS- and a TBSO-group in the *meta*-position are satisfactory coupling partners. They afforded the optically pure products **3d** and **3e** in 63−77% yield (dr = 99:1, 99% *ee*, entries 3−4). The arylation of **1** with (6-methoxynaphthalen-2-yl)zinc chloride (**2f**) and the benzodioxolylzinc reagent **2g** gave the lactone derivatives **3f** and **3g** in 61−84% yield (dr = 99:1, 99% *ee*, entries 5−6). Interestingly, the sterically hindered organozinc chloride **2h**, having a benzyloxy substituent in the *ortho*-position, was efficiently coupled with α-bromolactone **1**. The arylated lactone **3h** was obtained in 94% yield; dr = 99:1; 99% *ee* (entry 7).

Starting from L-threonine and pivalaldehyde, the chiral α-bromolactone **4** was prepared, bearing a smaller methyl substituent in the β-position.[8] The cross-coupling of **4** with various arylzinc reagents of type **2** was performed (Table 3). Thus, *p*-anisylzinc chloride **2a** led to the desired product **5a** in 81% yield (dr = 99:1, 99% *ee*). Similarly, *p*-trifluoromethoxyphenylzinc chloride **2b** and the electron-poor trifluoromethyl-substituted arylzinc reagent **2c** underwent the coupling reaction affording the protected β-hydroxy ester derivatives **5b** and **5c** (dr = 99:1, 99% *ee*) in 61−63% yield (entries 2−3). This arylation also proceeded well with *meta*-substituted zinc organometallics, such as the TBS-protected phenol (**2e**) and thioanisylzinc chloride (**2d**). The corresponding arylated esters **5d** and **5e** were obtained in 61−69% yield (dr = 99:1, 99% *ee*, entries 4−5). Methoxynaphthylzinc chloride **2f** and benzodioxolylzinc chloride **2g** stereoselectively arylated the α-bromolactone **4**, leading to the protected β-hydroxy esters **5f** and **5g** in 73−82% yield (dr = 99:1, 99% *ee*, entries 6−7).

Also, the zinc organometallics **2i** and **2j** bearing an ester function in the *meta*- and *para*-position were satisfactory coupling partners, leading to **5h** and **5i** in 52−76% yield (entries 8−9). The *meta*-carbethoxyphenylzinc chloride **2j**

Table 3. Stereoselective Cobalt-Catalyzed Cross-Couplings of Arylzinc Reagents of Type 2 with α-Bromolactone 4 Leading to Protected β-Hydroxy Esters of Type 5



entry	arylzinc reagent	product	yield[a]
1	 **2a**	 **5a**	81%
2	 **2b**	 **5b**	63%
3	 **2c**	 **5c**	61%
4	 **2e**	 **5d**	69%
5	 **2d**	 **5e**	61%
6	 **2f**	 **5f**	82%
7	 **2g**	 **5g**	73%
8	 **2i**; *para*	 **5h**; *para*	*para*: 76%[b]
9	**2j**; *meta*	**5i**; *meta*	*meta*: 52%

[a]Isolated yield of analytically pure products of type **5**. [b]dr = 50:50.

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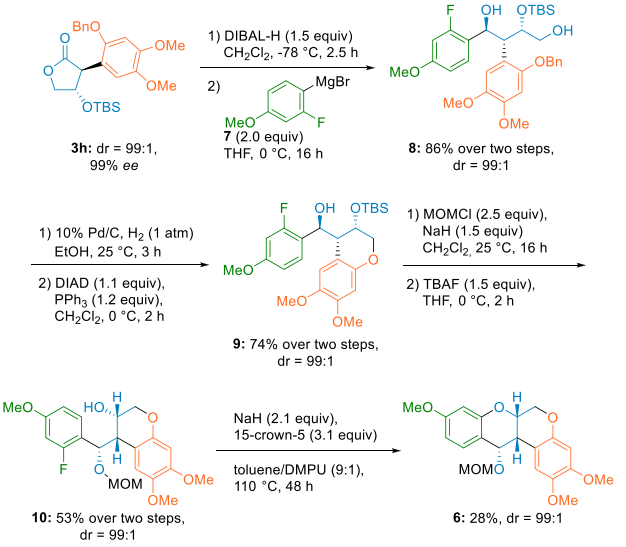
Scheme 1. Total Synthesis of the Artificial Rotenoid Derivative MOM-Protected Munduserol (6)



gave the product in excellent diastereomeric ratio (dr = 99:1). However, an ester substituent in the *para*-position resulted in epimerization in the course of the reaction (dr = 50:50). This can be explained by a subsequent base-catalyzed epimerization of the very acidic proton in the α-position to the aryl substituent in **5h**.

Many naturally occurring rotenoids and their structurally closely related unnatural derivatives show considerable antiplasmodial or cytotoxic activities.[10] These bioactive compounds were the target of several total syntheses.[11] Using this new Co-catalyzed arylation, we have prepared MOM-protected munduserol **6**, an artificial rotenoid derivative starting from the α-arylated lactone **3h** (Scheme 1). Thus, **3h** was reduced to the lactol with DIBAL-H and trapped with 2-fluoro-4-methoxyphenylmagnesium chloride (**7**). Interestingly, the diol **8** was obtained as a single diastereomer in 86% yield over two steps (dr = 99:1).[12] Next, the benzyl protecting group of **8** was removed via a palladium-catalyzed hydrogenolysis.[13] A selective Mitsunobu reaction allowed the first ring closure, affording the desired product **9** in 74% yield over two steps (dr = 99:1). Protection of **9** with MOMCl and deprotection of the silyl group with TBAF furnished **10** in 53% yield over two steps (dr = 99:1). Deprotonation of the secondary alcohol under forcing reaction conditions allowed the second ring closure via an intramolecular nucleophilic aromatic substitution. The MOM-protected munduserol **6** was obtained in 28% yield (dr = 99:1).

In conclusion, a highly *trans*-diastereoselective cobalt-catalyzed cross-coupling of arylzinc reagents with α-bromolactones bearing a substituent in the β-position was developed. α-Arylated butyrolactones and α-arylated protected β-hydroxy esters were obtained in the presence of 10–20% $CoCl_2$ and 10–20% PPh_3 in THF under mild conditions (25 °C, 16 h) in 52–96% yield (dr = 99:1, 99% *ee*). A stereoselective synthesis of an artificial rotenoid derivative MOM-protected munduserol (**6**) was performed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04564.

Full experimental details, ^1H and ^{13}C NMR spectra (PDF)

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Author Contributions

†M.S.H. and A.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; Wiley-VCH: Weinheim, Germany, 2010. (b) Yeh, V.; Szabo, W. A. Asymmetric Cross-Coupling Reactions. In *Applications of Transition Metal Catalysis in Drug Discovery and Development*; Crawley, M. L., Trost, B. M., Eds.; John Wiley and Sons: 2012; pp 165–213. (c) *Innovative Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; Wiley-VCH: Weinheim, Germany, 2015.

(2) (a) Horibe, H.; Fukuda, Y.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701–10709. (b) Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593–2595. (c) Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *2011*, 2761–2765. (d) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006. (e) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105. (f) Wang, C.-Y.; Derosa, J.; Biscoe, M. R. *Chem. Sci.* **2015**, *6*, 5105–5113. (g) Eno, M. S.; Lu, A.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138*, 7824–7827. (h) Yang, X.; Xu, G.; Tang, W. *Tetrahedron* **2016**, *72*, 5178–5183. (i) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153–3160. (j) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 5684–5687. (k) Uozumi, Y.; Matsuura, Y.; Suzuka, T.; Arakawa, T.; Yamada, Y. M. A. *Synthesis* **2016**, *49*, 59–68. (l) Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181–15185. (m) Huang, W.; Hu, M.; Wan, X.; Shen, Q. *Nat. Commun.* **2019**, *10*, 2963. (n) Jin, Y.; Wang, C. *Angew. Chem., Int. Ed.* **2019**, *58*, 6722–6726. (o) Wang, G.; Xin, X.; Wang, Z.; Lu, G.; Ma, Y.; Liu, L. *Nat. Commun.* **2019**, *10*,

https://dx.doi.org/10.1021/acs.orglett.9b04564
Org. Lett. XXXX, XXX, XXX−XXX

559. (p) Aparece, M. D.; Hu, W.; Morken, J. P. *ACS Catal.* **2019**, *9*, 11381−11385.
(3) World market prices for Pd: 51140 EUR/kg; for Co: 32 EUR/kg (retireved Nov. 2019, http://www.infomine.com).
(4) (a) *Handbook on the Toxicology of Metals*; Friberg, L., Nordberg, G. F., Vouk, V. B., Eds.; Elsevier: Amsterdam, 1986. (b) Egorova, K. S.; Ananikov, V. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 12150−12162.
(5) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435−1462.
(6) (a) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, *2009*, 2931−2934. (b) Gülak, S.; Stepanek, O.; Malberg, J.; Rad, B. R.; Kotora, M.; Wolf, R.; Jacobi von Wangelin, A. *Chem. Sci.* **2013**, *4*, 776−784. (c) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 17662−17668. (d) Liu, F.; Bian, Q.; Mao, J.; Gao, Z.; Liu, D.; Liu, S.; Wang, X.; Wang, Y.; Wang, M.; Zhong, J. *Tetrahedron: Asymmetry* **2016**, *27*, 663−669. (e) Rérat, A.; Michon, C.; Agbossou-Niedercorn, F.; Gosmini, C. *Eur. J. Org. Chem.* **2016**, *2016*, 4554−4560. (f) Barde, E.; Guérinot, A.; Cossy, J. *Org. Lett.* **2017**, *19*, 6068−6071. (g) Liu, F.; Zhong, J.; Zhou, Y.; Gao, Z.; Walsh, P. J.; Wang, X.; Ma, S.; Hou, S.; Liu, S.; Wang, M.; Wang, M.; Bian, Q. *Chem. - Eur. J.* **2018**, *24*, 2059−2064. (h) Thomas, L.; Lutter, F. H.; Hofmayer, M. S.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2018**, *20*, 2441−2444. (i) Linke, S.; Manolikakès, S. M.; Auffrant, A.; Gosmini, C. *Synthesis* **2018**, *50*, 2595−2600. (j) Lutter, F. H.; Graßl, S.; Grokenberger, L.; Hofmayer, M. S.; Chen, Y.-H.; Knochel, P. *ChemCatChem* **2019**, *11*, 5188−5197. (k) Sun, X.; Wang, X.; Liu, F.; Gao, Z.; Bian, Q.; Wang, M.; Zhong, J. *Chirality* **2019**, *31*, 682−687. (l) Dorval, C.; Dubois, E.; Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. *Adv. Synth. Catal.* **2019**, *361*, 1777−1780. (m) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 6241−6244. (n) Song, T.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 603−607.
(7) (a) Hammann, J. M.; Haas, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 4478−4481. (b) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540−1552. (c) Haas, D.; Hammann, J. M.; Lutter, F. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 3809−3812. (d) Hammann, J. M.; Hofmayer, M. S.; Lutter, F. H.; Thomas, L.; Knochel, P. *Synthesis* **2017**, *49*, 3887−3894. (e) Hammann, J. M.; Lutter, F. H.; Haas, D.; Knochel, P. *Angew. Chem.* **2017**, *129*, 1102−1106. (f) Hammann, J. M.; Thomas, L.; Chen, Y.-H.; Haas, D.; Knochel, P. *Org. Lett.* **2017**, *19*, 3847−3850. (g) Hofmayer, M. S.; Hammann, J. M.; Lutter, F. H.; Knochel, P. *Synthesis* **2017**, *49*, 3925−3930. (h) Li, J.; Knochel, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 11436−11440. (i) Balkenhohl, M.; Ziegler, D. S.; Desaintjean, A.; Bole, L. J.; Kennedy, A. R.; Hevia, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2019**, *58*, 12898−12902. (j) Graßl, S.; Hamze, C.; Koller, T. J.; Knochel, P. *Chem. - Eur. J.* **2019**, *25*, 3752−3755. (k) Lutter, F. H.; Grokenberger, L.; Hofmayer, M. S.; Knochel, P. *Chem. Sci.* **2019**, *10*, 8241−8245. (l) Lutter, F. H.; Hofmayer, M. S.; Hammann, J. M.; Malakhov, V.; Knochel, P. Generation and Trapping of Functionalized Aryl- and Heteroarylmagnesium and -Zinc Compounds. In *Organic Reactions*; Denmark, E. S., Ed.; Wiley: 2019; Vol. *100*, pp 63−120.
(8) (a) Hammann, J. M.; Steib, A. K.; Knochel, P. *Org. Lett.* **2014**, *16*, 6500−6503. (b) Hammann, J. M.; Haas, D.; Steib, A. K.; Knochel, P. *Synthesis* **2015**, *47*, 1461−1468.
(9) See Supporting Information.
(10) (a) Fang, N.; Casida, J. E. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 3380. (b) Fang, N.; Casida, J. E. *J. Agric. Food Chem.* **1999**, *47*, 2130−2136. (c) Yenesew, A.; Derese, S.; Midiwo, J. O.; Oketch-Rabah, H. A.; Lisgarten, J.; Palmer, R.; Heydenreich, M.; Peter, M. G.; Akala, H.; Wangui, J.; Liyala, P.; Waters, N. C. *Phytochemistry* **2003**, *64*, 773−779. (d) Ahmed-Belkacem, A.; Macalou, S.; Borrelli, F.; Capasso, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Di Pietro, A. *J. Med. Chem.* **2007**, *50*, 1933−1938. (e) Varughese, R. S.; Lam, W. S.-T.; Marican, A. A. b. H.; Viganeshwari, S. H.; Bhave, A. S.; Syn, N. L.; Wang, J.; Wong, A. L.-A.; Kumar, A. P.; Lobie, P. E.; Lee, S. C.; Sethi, G.; Goh, B. C.; Wang, L. *Cancer* **2019**, *125*, 1789−1798.
(11) (a) Nakatani, N.; Matsui, M. *Agric. Biol. Chem.* **1968**, *32*, 769−772. (b) Granados-Covarrubias, E. H.; Maldonado, L. A. *J. Org. Chem.* **2009**, *74*, 5097−5099. (c) Nayak, M.; Kim, I. *J. Org. Chem.* **2015**, *80*, 11460−11467. (d) Georgiou, K. H.; Pelly, S. C.; de Koning, C. B. *Tetrahedron* **2017**, *73*, 853−858. (e) Nakamura, K.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 182−187. (f) Matsuoka, S.; Nakamura, K.; Ohmori, K.; Suzuki, K. *Synthesis* **2019**, *51*, 1139−1156. (g) Perveen, S.; Yang, S.; Meng, M.; Xu, W.; Zhang, G.; Fang, X. *Commun. Chem.* **2019**, *2*, 8.
(12) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1224. (b) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433−9441.
(13) Hartung, W. H.; Simonoff, R. Hydrogenolysis of Benzyl Groups Attached to Oxygen, Nitrogen, or Sulfur. *Organic Reactions*; John Wiley and Sons: 1953; pp 263−326.

https://dx.doi.org/10.1021/acs.orglett.9b04564
Org. Lett. XXXX, XXX, XXX−XXX