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Synthesis of Chiral Esters via Asymmetric Wolff Rearrangement Reaction

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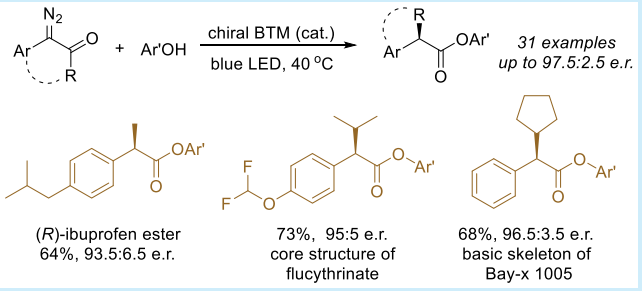
Supporting Information

ABSTRACT: The first asymmetric Wolff rearrangement reaction that directly converts α-diazoketones into broadly useful chiral α,α-disubstituted carboxylic esters with high enantioselectivities (up to 97.5:2.5 er) is reported. The cascade reaction proceeds through the seamless combination of visible-light-induced formation of the ketene intermediate and asymmetric ketene esterification using a readily available benzotetramisole-type catalyst.



Chiral carboxylic acid derivatives bearing two or more substituents at the α-carbons are important bioactive molecules. For instance, ibuprofen and other similar propionic acid derivatives are widely used nonsteroidal anti-inflammatory drugs. Flucythrinate is a pyrethroid insecticide and acaricide, and clidanac is used to treat rheumatoid arthritis (Figure 1).[1] As such, the synthesis and transformations of these compounds are of high importance.

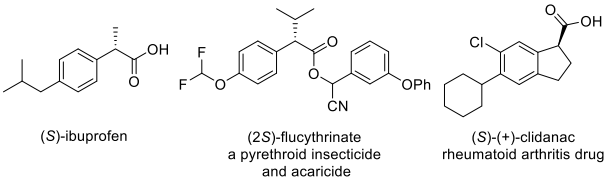
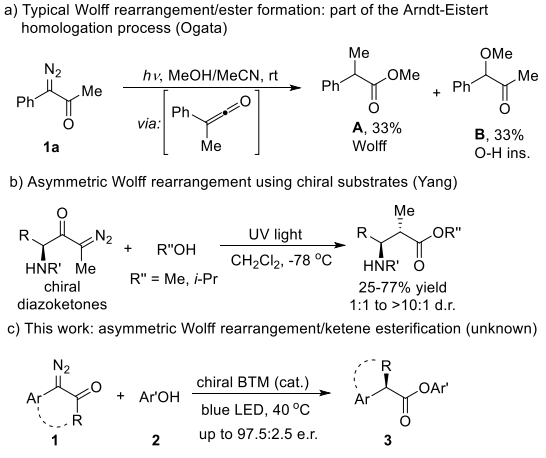


Figure 1. Examples of bioactive α, α-disubstituted carboxylic acid derivatives.

Wolff rearrangement,[2] the transformation of α-diazoketones to ketenes, provides a practical method for the synthesis of carboxylic acid derivatives when conducted in the presence of nucleophiles such as water, alcohols, or amines.[3] The cascade processes from α-diazoketones to carboxylic acid derivatives, which are often regarded as Wolff rearrangement reactions as well,[4] are particularly useful in the Arndt−Eistert homologations as a one-carbon (methylene) extension method.[3d] However, to the best of our knowledge, the catalytic asymmetric transformation from achiral α-diazoketones to chiral carboxylic acid derivatives is still unknown. The challenges are not only the stereocontrol of the nucleophilic addition to ketenes but also to avoid the side reactions such as O−H and C−H insertions to the carbene intermediate. As a typical example, light-induced Wolff rearrangement of α-diazoketone **1a** in the presence of methanol led to a 1:1 mixture of the Wolff product and the O−H insertion product (Scheme 1a).[3a] Yang reported the asymmetric Wolff rearrangement reaction using chiral diazoketones to give chiral β-amino acid esters in poor to moderate yields and up to 10:1 diastereoselectivities (Scheme 1b).[4] On the other hand, more effects have been focused on the more reactive ketene substrates via organocatalysis to prepare chiral α,α-disubstituted carboxylic acid derivatives.[5] Pracejus first reported the asymmetric addition of methanol to methylphenylketene catalyzed by brucine and quinine derivatives at −110 °C with moderate enantioselectivity.[6] Applying planar-chiral

Scheme 1. Wolff Rearrangement for the Synthesis of α,α-Disubstituted Carboxylic Acid Derivatives



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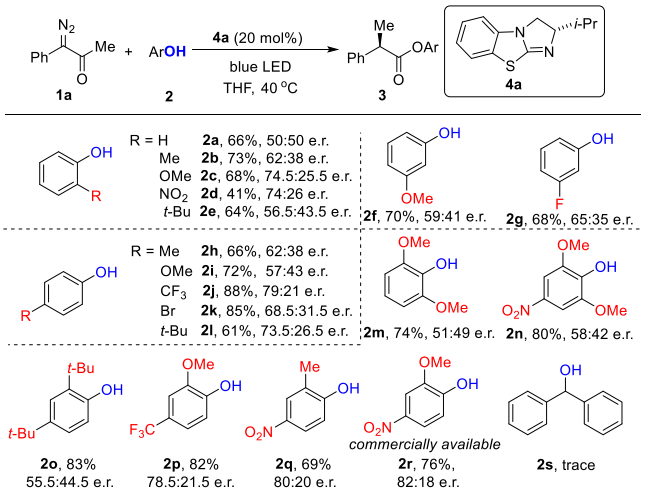
DMAP drivatives, Fu's group reported the highly enantioselective esterifications of alkylarylketenes with methanol, phenols, and enolizable diphenylacetaldehydes.[7] Ye[8] and Smith[9] have pioneered the NHC[10]-catalyzed asymmetric ketene esterifications with moderate to excellent enantioselectivities. Though with high enantioselectivities and broad substrate scope, due to the instability of ketene substrates, the widespread applications of these otherwise ideal methods are restricted. Dynamic kinetic resolution of carboxylic acids and their derivatives, represented by Birman,[11] Shiina,[12] and Chi's[13] work, also features highly enantioselective and with high yields but inevitably requires the presynthesis of the racemic α,α-disubstituted carboxylic acids derivatives and often demands an excess amount of bases or activation reagents. Herein, with our continuous research interest in asymmetric cascade reactions[14] and inspired by recent progresses in the area of Wolff rearrangement,[2c,15] we report the first catalytic asymmetric Wolff rearrangement reaction of achiral α-diazoketones to give chiral α,α-disubstituted carboxylic acid esters with high enantioselectivities (up to 97.5:2.5 er) (Scheme 1c).

The structure of the nucleophile has a significant influence on the enantioselectivity of the ketene nucleophilic addition reaction. Thus, our investigation was initiated with the screening for ideal oxygen nucleophiles (Scheme 2). Blue

Scheme 2. Evaluation of Phenols and Diphenylmethanol[a]

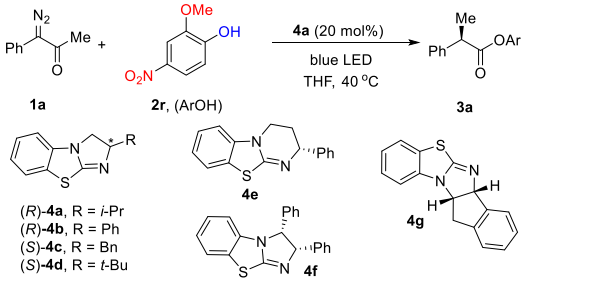


[a]Unless indicated otherwise, the reaction of **1** (0.1 mmol) and **2** (0.2 mmol) were carried out with **4c** (20 mol %), in 2-methyltetrahydrofuran (2.0 mL) at 40 °C under irradiation of blue LEDs for 16 h.

LED was applied for the light-induced Wolff rearrangement,[3c] which features mild conditions and high yield, to generate the ketene intermediate. The reaction of phenol **2a** and 1-diazo-1-phenylacetone **1a** in the presence of a nucleophilic benzotetramisole-type catalyst[16,17] **4a** led to the desired product in 66% yield, but no enantioselectivity was observed. The presence of a substituent at the ortho position of the phenol could render the reaction enantioselectivities (**2b**–**2e**), and a methoxyl group resulted in the highest enantioselectivity (**2c**), whereas the presence of a bulky *tert*-butyl group only led to poor enantioselectivity (**2e**). Comparatively, functional groups at the meta position of the phenol had much less effect on the stereoselectivity of the reaction (**2f**–**2g**). Later on, the examination of the substituents at the para position (**2h**–**2l**) revealed that the incorporation of either an electron-withdrawing group (**2j** and **2k**) or a bulky group (**2l**) at the para position all resulted in higher enantiomeric ratio. 2,6-Disubstituted phenols **2m** and **2n** all led to the corresponding product with poor enantioselectivity. Based on the above results, our investigation was focused on 2,4-disubstituted phenols (**2o**–**2r**). Gratifyingly, phenols with an electron-donating group at the ortho position and an electron-withdrawing group at the para position are optimal substrates for the reaction, regarding both enantioselectivity and the yield (**2p**–**2r**). Phenol **2r**, a commercially available compound, gave the corresponding chiral ester in 76% yield and 82:18 enantiomeric ratio. Diphenylmethanol **2s**, a frequently used alcohol for the dynamic kinetic resolution of carboxylic acids or esters,[8,13] only led to a trace amount of product.

With the optimal oxygen nucleophile **2r** identified, the reaction conditions were further optimized first through the screening of chiral nucleophilic catalysts (Table 1). The results

Table 1. Reaction Optimization[a]



entry	solvent	4	T (°C)	yield[b] (%)	er[c]
1	THF	**4a**	40	76	82:18
2	THF	**4b**	40	63	58.5:41.5
3	THF	**4c**	40	62	88.5:11.5
4	THF	**4d**	40	43	50:50
5	THF	**4e**	40	71	53:47
6	THF	**4f**	40	53	60.5:39.5
7	THF	**4g**	40	68	58.5:41.5
8	MTBE	**4c**	40	70	90:10
9	DME	**4c**	40	60	91:9
10	2-Me-THF	**4c**	40	65	92.5:7.5
11	2-Me-THF	**4c**	**40**	**80**[d]	**93:7**

[a]Unless indicated otherwise, the reaction of **1** (0.1 mmol) and **2** (0.2 mmol) was carried out with **4c** (20 mol %) in 2-methyltetrahydrofuran (2.0 mL) at 40 °C under irradiation of blue LEDs for 16 h. [b]Determined by ^{1}H NMR analysis of the crude reaction product. [c]Determined by chiral HPLC. [d]Isolation yield.

revealed that the enantiomeric ratio of **3a** was significantly affected by the structure of the Birman-type chiral Lewis bases (entries 1–7). Notably, whereas the *tert*-butyl substituted catalyst (*S*)-**4d** (entry 4) gave racemic product, (*S*)-**4c** bearing a benzyl group (entry 3) proved to be the optimal catalyst regarding of the enantioselectivity. Of note, a number of chiral NHCs were also evaluated in the presence of additional base. However, while up to 70% yield could be achieved, only poor enantioselectivities were observed (see the Supporting Information for details). A thorough examination of solvents showed that ethers were ideal media for the cascade reaction, and 2-Me THF gave the product with the highest enantiomeric ratio (entry 10, see the Supporting Information for more results). Further, performing the reaction at lower concen-

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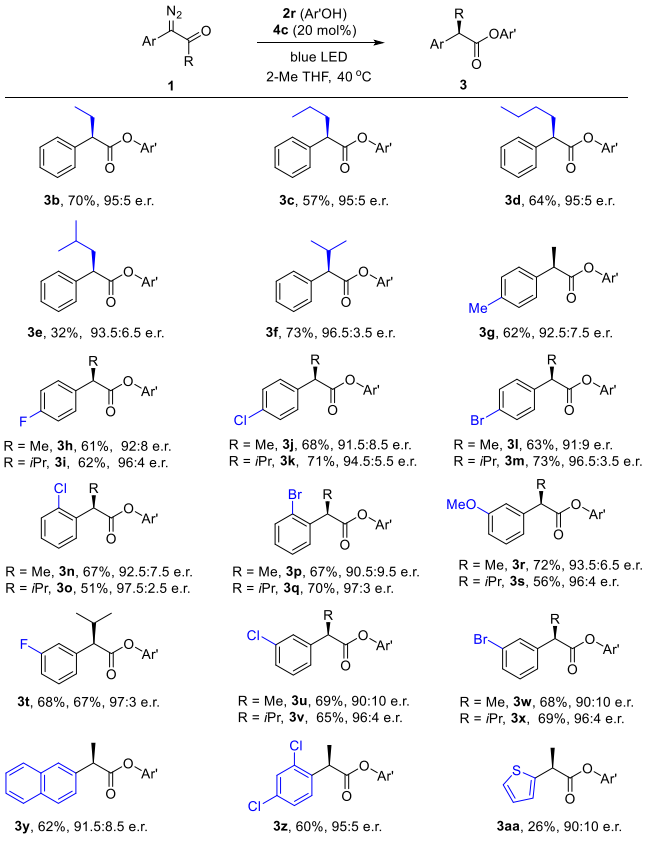
tration could further improve the yield to 80% and the enantiomeric ratio to 93:7 (entry 11).

The optimized reaction conditions were first applied to an array of α-diazoketones bearing various alkyl groups in the reaction with phenol **3r** (Scheme 3). Generally, a range of alkyl

Scheme 3. Substrate Scope[a]

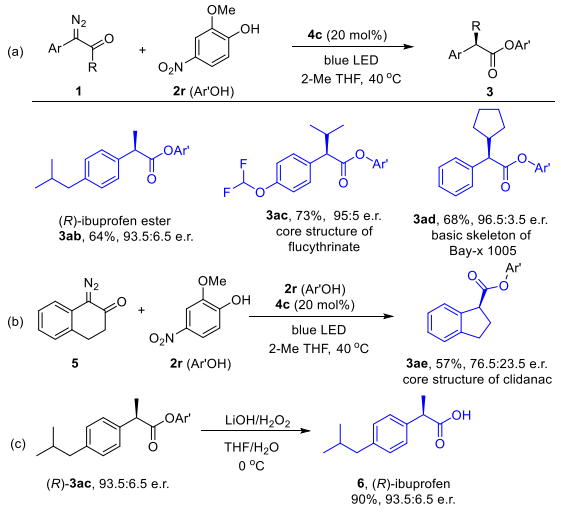


[a]Unless indicated otherwise, the reaction of **1** (0.1 mmol) and **2** (0.2 mmol) were carried out with **4c** (20 mol %) in 2-methyltetrahydrofuran (2.0 mL) at 40 °C under irradiation of blue LEDs for 16 h.

groups could be well tolerated, giving the corresponding chiral esters with high to excellent enantioselectivities (**3b**−**3f**). Noteworthy, isopropyl-substituted substrate is preferable to achieve higher stereoselectivity (**3f**, 96.5:3.5 er). The scope of the aryl groups were then examined through the reactions of **2r** with α-aryl-α-diazomethylisopropylketones and α-aryl-α-diazoacetones. For all of the tested α-aryl-α-diazoketones, high to excellent enantioselectivities could be obtained. The substitution pattern of the aryl ring of the α-aryl-α-diazoketones, either para (**3g**−**3m**), ortho (**3n**−**3q**), or meta (**3r**−**3x**), and the electronic properties of the substituent as well, exhibited very limited effect on the yield and enantioselectivity of the reaction. Other aryl groups, such as 2-naphthyl (**3y**) and 2, 4-dichlorophenyl (**3z**), are also tolerated, affording the desired product with moderate to good yield and high enantioselectivity. Substrate bearing a heterocycle (i.e., 2-thiophene-yl) also gave the correct product with high er but in much lower yield (**3aa**). The low yield might be due to undesired reactions associated with the electron-rich thiophene moiety.

The asymmetric Wolff rearrangement reaction may offer an effective way for the preparation of bioactive α-alkyl-α-arylcarboxylic acid derivatives. As illustrated in Scheme 4a,

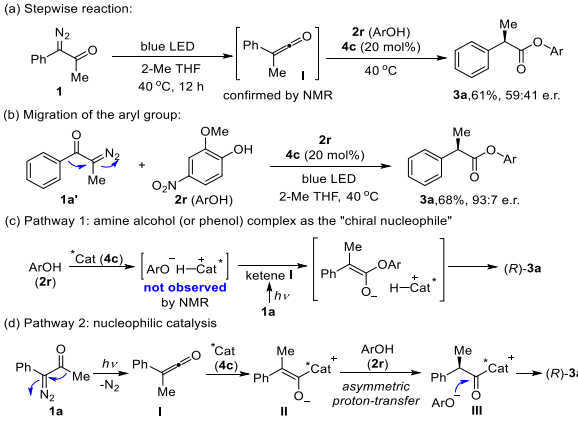
Scheme 4. Employing the Current Asymmetric Wolff Rearrangement Reaction for the Synthesis of Bioactive Compounds



(*R*)-ibuprofen ester **3ab**, **3ac** bearing a difluoromethoxyl group at the para position (the core structure of flucythrinate) and **3ad** (the basic skeleton of lipoxygenase inhibitor Bay-x 1005)[18] could be afforded through the cascade reaction with high to excellent enantioselectivities. With a cyclic α-diazo ketone substrate, Wolff rearrangement could provide the one-carbon ring-contracted product.[19] Under the standard reaction conditions, 1-diazo-2-tetrlong **5** could also undergo the cascade reaction to give chiral 1-indancarboxylic acid ester, the core structure of clidanac,[1a] albeit with moderate yield and enantioselectivity (Scheme 4b). The ester group of the product (e.g., **3ab**) can be easily removed by using the well-established method in high yield (Scheme 4c).

Control experiments were performed to further understand the mechanism of the reaction (Scheme 5). Visible-light

Scheme 5. Control Experiments and Proposed Mechanism for the Reaction



irradiation of α-diazoketone **1a** alone overnight led to complete conversion to phenyl methyl ketene **I**, which was confirmed by NMR analysis. One-pot addition of phenol **2r** in the presence of catalyst **4c** afforded **3a** in 61% yield and 59:41 er (Scheme 5a). The severe decrease of the enantioselectivity implies the existence of an uncatalyzed racemic background reaction. On the other hand, under our cascade reaction

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conditions, the reactive ketene intermediate is generated slowly and directly trapped by the nucleophic catalyst, leading to the chiral product with high stereoselectivity. Under the standard reaction conditions, compared to substrate **1a**, α-diazoketone **1a′** could undergo aryl-migrative Wolff rearrangement, generating the same phenyl methyl ketene **I**, and provided chiral ester **3a** with identical enantioselectivity and slightly lower yield (Scheme 5b). The above results all support that the reaction proceeds through the ketene intermediate. As for the chiral amine-catalyzed ketene esterification step, it is widely accepted that there could be two mechanistic pathways:[7c,9,20] (1) initial formation of an amine alcohol (phenol) complex as a "chiral nucleophile", which reacts with the ketene cabonyl (Scheme 5c), and (2) nucleophilic attack of the amine catalyst to the ketene to form a C1 ammonium enolate[21] intermediate, which undergoes an asymmetric proton-transfer process with the phenol (Scheme 5d). When phenol **2r** and catalyst **4c** are mixed, there is no evidence by ^{1}H NMR for formation of an ion pair, which was observed in the chiral DMAP-catalyzed addition of phenol to ketenes reported by Fu.[7c] This is probably due to the weaker basity of the benzotetramisole-type catalyst. As such, the second pathway of nucleophilic catalysis is highly favored for the current reaction.

In conclusion, we have developed the first asymmetric Wolff rearrangement reaction that directly transforms α-diazoketones into chiral esters using a commercially available phenol derivative. The cascade reaction consists of a visible-light-induced Wolff rearrangement, which slowly generates the ketene intermediate, and subsequent chiral benzotetramisole-catalyzed asymmetric ketene esterification. The current method allows for effective access to the broadly useful α,α-disubstituted carboxylic esters with up to 97.5:2.5 er.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03227.

Complete experimental procedures and characterization data for the prepared compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Noguchi, S.; Kishimoto, S.; Minamida, I.; Obayashi, M.; Kawakita, K. *Chem. Pharm. Bull.* **1971**, *19*, 646−648. (b) Bodor, N.; Woods, R.; Raper, C.; Kearney, P.; Kaminski, J. J. *J. Med. Chem.* **1980**, *23*, 474−480. (c) Addor, R.; Berkelhammer, G. In *Annual Reports in Medicinal Chemistry*; Hess, H.-J., Ed.; Academic Press, 1982; Vol. *17*, pp 311−321.

(2) (a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *2002*, 2193−2256. (b) Coquerel, Y.; Rodriguez, J.. In *Molecular Rearrangements in Organic Synthesis*; Wiley, 2015; pp 59−84. (c) Ciszewski, L. W.; Rybicka-Jasinska, K.; Gryko, D. *Org. Biomol. Chem.* **2019**, *17*, 432−448. (d) Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, *45*, 5278−5283. (e) Csizmadia, I. G.; Font, J.; Strausz, O. P. *J. Am. Chem. Soc.* **1968**, *90*, 7360−7361. (f) Cui, G.; Thiel, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 433−436. (g) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129−195.

(3) (a) Ogata, Y.; Sawaki, Y.; Ohno, T. *J. Am. Chem. Soc.* **1982**, *104*, 216−219. (b) Tomioka, H.; Okuno, H.; Kondo, S.; Izawa, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7123−7125. (c) Bernardim, B.; Hardman-Baldwin, A. M.; Burtoloso, A. C. B. *RSC Adv.* **2015**, *5*, 13311−13314. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.

(4) Yang, H.; Foster, K.; Stephenson, C. R. J.; Brown, W.; Roberts, E. *Org. Lett.* **2000**, *2*, 2177−2179.

(5) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771−6803.

(6) Pracejus, H. *Justus. Liebigs. Ann. Chem.* **1960**, *634*, 9.

(7) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (b) Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606−4608. (c) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176−6177. (d) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007.

(8) Wang, X. N.; Lv, H.; Huang, X. L.; Ye, S. *Org. Biomol. Chem.* **2009**, *7*, 346−350.

(9) Concellón, C.; Duguet, N.; Smith, A. D. *Adv. Synth. Catal.* **2009**, *351*, 3001−3009.

(10) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988−3000. (c) Liu, B.; Yan, J.; Huang, R.; Wang, W.; Jin, Z.; Zanoni, G.; Zheng, P.; Yang, S.; Chi, Y. R. *Org. Lett.* **2018**, *20*, 3447−3450.

(11) (a) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9638−9642. (b) Yang, X.; Birman, V. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 5553−5555.

(12) Shiina, I.; Ono, K.; Nakata, K. *Catal. Sci. Technol.* **2012**, *2*, 2200−2205.

(13) Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* **2016**, *138*, 7212−7215.

(14) (a) Li, L. L.; Ding, D.; Song, J.; Han, Z. Y.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2019**, *58*, 7647−7651. (b) Meng, J.; Fan, L.-F.; Han, Z.-Y.; Gong, L.-Z. *Chem.* **2018**, *4*, 1047−1058. (c) Meng, J.; Li, X.-H.; Han, Z.-Y. *Org. Lett.* **2017**, *19*, 1076−1079.

(15) (a) Liu, D.; Ding, W.; Zhou, Q. Q.; Wei, Y.; Lu, L. Q.; Xiao, W. J. *Org. Lett.* **2018**, *20*, 7278−7282. (b) Li, M.-M.; Wei, Y.; Liu, J.; Chen, H.-W.; Lu, L.-Q.; Xiao, W.-J. *J. Am. Chem. Soc.* **2017**, *139*, 14707−14713. (c) Liu, J.; Li, M. M.; Qu, B. L.; Lu, L. Q.; Xiao, W. J. *Chem. Commun.* **2019**, *55*, 2031−2034.

(16) (a) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.* **2016**, *2016*, 5589−5610. (b) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351−1354. (c) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115−1118. (d) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301−2304. (e) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714−2720. (f) Simal, C.; Lebl, T.; Slawin, A. M.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653−3657.

(17) (a) Schwarz, K. J.; Yang, C.; Fyfe, J. W. B.; Snaddon, T. N. *Angew. Chem., Int. Ed.* **2018**, *57*, 12102−12105. (b) Schwarz, K. J.; Pearson, C. M.; Cintron-Rosado, G. A.; Liu, P.; Snaddon, T. N. *Angew. Chem., Int. Ed.* **2018**, *57*, 7800−7803. (c) Spoehrle, S. S. M.; West, T. H.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2017**, *139*, 11895−11902. (d) Jiang, X.; Beiger, J. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 87−90. (e) Schwarz, K. J.; Amos, J. L.; Klein, J. C.; Do, D. T.; Snaddon, T. N. *J. Am. Chem. Soc.* **2016**, *138*, 5214−5217. (f) Song, J.; Zhang, Z. J.; Chen, S. S.; Fan, T.; Gong, L. Z. *J. Am. Chem. Soc.* **2018**, *140*, 3177−3180. (g) Song, J.; Zhang, Z. J.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 5212−5216.

(18) Hatzelmann, A.; Fruchtmann, R.; Mohrs, K. H.; Raddatz, S.; Müller-Peddinghaus, R. *Biochem. Pharmacol.* **1993**, *45*, 101−111.

DOI: 10.1021/acs.orglett.9b03227
Org. Lett. XXXX, XXX, XXX−XXX

(19) Lowe, G.; Ridley, D. D. *J. Chem. Soc., Chem. Commun.* **1973**, 328−329.
(20) (a) Brady, W. T.; Vaughn, W. L.; Hoff, E. F. *J. Org. Chem.* **1969**, *34*, 843−845. (b) Tille, A.; Pracejus, H. *Chem. Ber.* **1967**, *100*, 196. (c) Lillford, P. J.; Satchell, D. P. N. *J. Chem. Soc. B* **1968**, 889−897. (d) Jähme, J.; Rüchardt, C. *Tetrahedron Lett.* **1982**, *23*, 4011−4014. (e) Cannizzaro, C. E.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 2668−2669.
(21) (a) Lectka, T.; France, S.; Guerin, D. J.; Miller, S. J. *Chem. Rev.* **2003**, *103*, 2985−3012. (b) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596−5605. (c) Smith, A.; Douglas, J.; Churchill, G. *Synthesis* **2012**, *44*, 2295−2309. (d) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214−622.

DOI: 10.1021/acs.orglett.9b03227
Org. Lett. XXXX, XXX, XXX−XXX