Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 2315−2319

pubs.acs.org/OrgLett

Aroyl Isocyanates as 1,4-Dipoles in a Formal [4 + 1]-Cycloaddition Approach toward Oxazolone Construction

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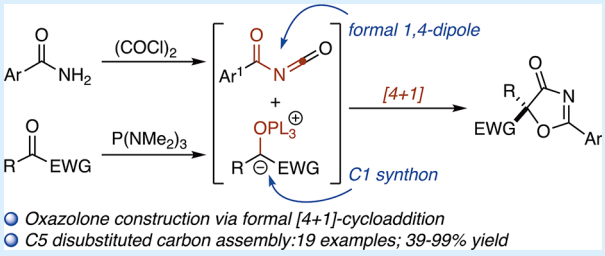
Supporting Information

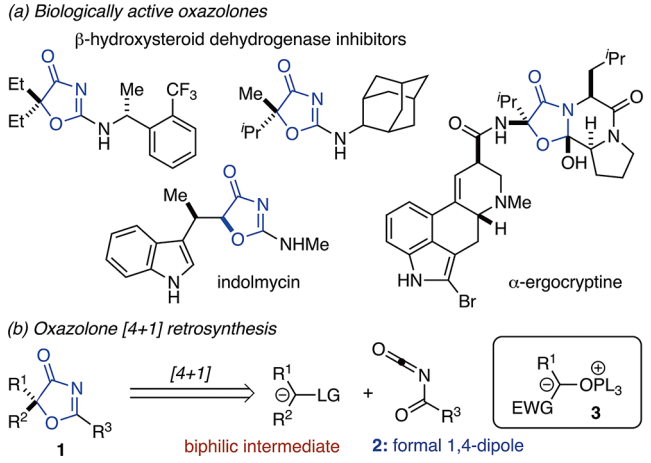
ABSTRACT: A formal phosphine-mediated [4 + 1]-cycloaddition between a 1,2-dicarbonyl and an aroyl isocyanate to provide oxazolones bearing a disubstituted C5 center is described. By exploiting the carbene-like reactivity of oxyphosphonium enolates as C1 synthons and aroyl isocyanates as formal 1,4-dipoles, oxazolones and spirooxindole oxazolones are constructed in high yields (39−99%).



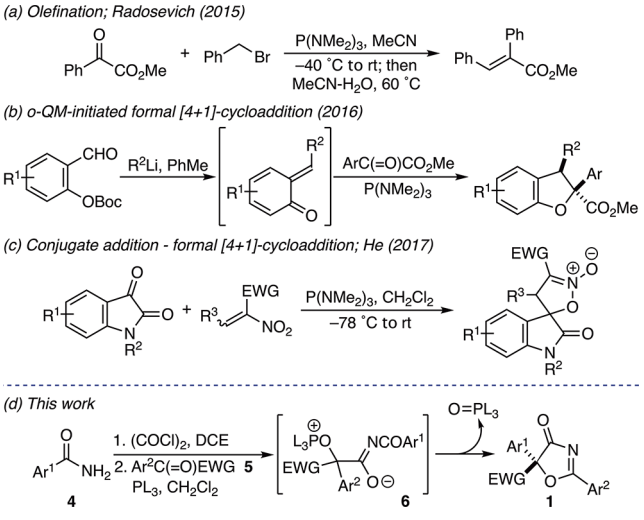
While five-membered heterocyclic frameworks have inspired synthetic and medicinal chemists alike for decades, the selective and convergent assembly of biologically active, highly substituted *N*- and *N*,*O*-mixed heterocycles remains a challenge in pharmaceutical drug development.[1] Notably, the 3-oxazolone subunit has recently drawn considerable interest from industry and academia as a core architecture prevalent across a diverse array of biologically active natural products and designed small molecules. For example, the oxazolone is a key architectural motif in a series of β-hydroxysteroid dehydrogenase inhibitors used to treat diabetes and obesity,[2] the broad spectrum antibiotic, *Streptomyces albus*-derived natural product indolmycin, and the ergot alkaloids α- and β-ergocryptine (Scheme 1a).[3] While perhaps the most widely employed method for assembling the oxazolone motif involves the intramolecular *O*-alkylation of α-halo imides,[4] more recent efforts have focused on establishing quaternary substitution at the C5 position (e.g., alkylations, [3 + 2]-cycloadditions, etc.).[4a,b,5−7] In contrast, a [4 + 1] retrosynthetic disconnect of oxazolone **1** at C5 reveals a disubstituted C1 synthon and an aroyl isocyanate **2** (Scheme 1b). Leveraging a recent resurgence in the literature of the Kukhtin−Ramirez reaction, we envisioned exploiting the biphilic reactivity of oxyphosphonium enolate **3** to assemble this versatile heterocyclic framework.

While Ramirez first reported the feasibility of C−C and C−O redox bond formations initiated by the addition of PL_3 to 1,2-dicarbonyls,[8] Radosevich has pioneered a renaissance of this disconnect, recently exemplified by the addition of α-ketoesters to alkyl halides (Scheme 2a). Subsequently, we demonstrated the feasibility of employing oxyphosphonium enolates as C1 synthons in a formal [4 + 1]-cycloaddition assembly of

Scheme 1. Biologically Active Oxazolones



Scheme 2. PL_3-Mediated Annulations



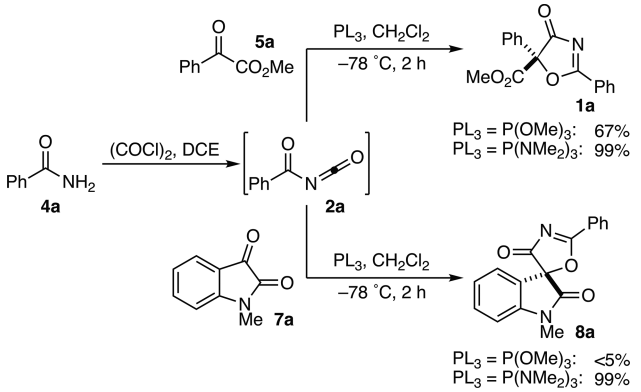
Received: February 24, 2018
Published: April 10, 2018

DOI: 10.1021/acs.orglett.8b00656
Org. Lett. 2018, 20, 2315−2319

dihydrobenzofurans from *in situ* generated *ortho*-quinone methides (Scheme 2b). Additionally, He and co-workers reported a similar strategy for the construction of isoxazoline *N*-oxides from nitro alkenes and isatin derivatives (Scheme 2c).[9−11] Inspired by these findings, and in continuation of our work on the [4 + 1] assembly of heterocyclic scaffolds, herein, we report the assembly of oxazolone **1**, wherein conversion of amide **4** to the corresponding aroyl isocyanate precedes addition of 1,2-dicarbonyl **5** facilitated by trivalent phosphorus (Scheme 2d). Subsequent *O*-alkylative redox cyclization of the presumptive intermediate **6** yields the desired cycloadduct.

Our initial investigation into the formal [4 + 1]-cycloaddition of 1,2-dicarbonyls with acyl isocyanates revealed an intriguing correlation between the nature of the trivalent phosphorus reagent and product yield. Treatment of benzamide with oxalyl chloride, followed by addition of α-ketoester **5a** and $P(OMe)_3$ at −78 °C to unpurified isocyanate **2a**, led to formation of oxazolone **1a** in 67% yield (Scheme 3). However, employing *N*-

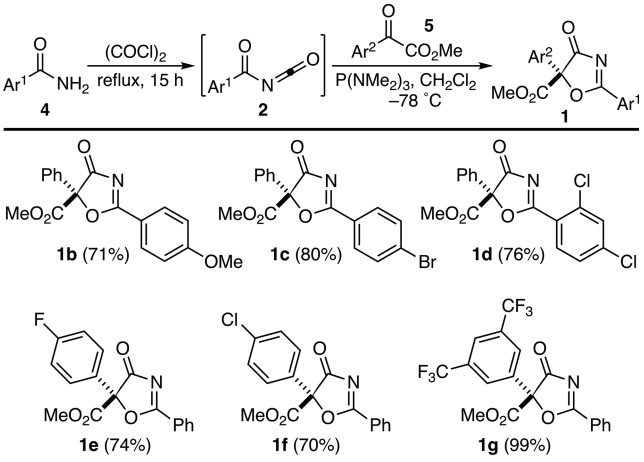
Scheme 3. Disparate Phosphorus Reactivity



methyl isatin (**7a**) in place of **5a** led to only trace amounts of spirooxazolone oxindole **8a**. Interestingly, we noticed little substrate dependence when $P(OMe)_3$ was replaced with the more electron-rich and sterically encumbered $P(NMe_2)_3$, resulting in near-quantitative yields of oxazolones **1a** and **8a** from α-ketoester **5a** and isatin **7a**, respectively. Consistent with previous work on Kukhtin−Ramirez-like C−X bond formations, allowing the reaction to reach higher temperatures resulted in significant self-condensation of the 1,2-dicarbonyl, and aliphatic solvents (e.g., hexanes, toluene, etc.) led to quantitative recovery of the starting materials.[12]

Based on the consistently high yields observed with $P(NMe_2)_3$ in CH_2Cl_2 at −78 °C, we chose to employ this optimal set of conditions to evaluate the formal [4 + 1]-cycloaddition of aryl formates **5** with benzamide derivatives **4** in the assembly of oxazolones **1** (Scheme 4). Electron-rich and -poor aroyl isocyanates underwent cycloaddition with **5a** to give the corresponding oxazolones **1b−d** in comparably good yields (71−80%). Additionally, 4-fluoro- and 4-chloro-substituted aryl formates provided oxazolones **1e** and **1f** in 74% and 70% yields, respectively. Consistent with our earlier observation that electron-deficient aryl formates were more reactive as [4 + 1]-cycloaddition C1 synthons than their electron-rich counterparts, the 3,5-bistrifluoromethyl phenyl-substituted α-ketoester gave oxazolone **1g** in 99% yield. It is noteworthy that this method is limited by the need for an aryl 1,2-dicarbonyl, as aliphatic formates failed to provide the desired cycloadducts. A similarly intractable mixture of byproducts was observed with

Scheme 4. Formal [4 + 1]-Cycloaddition Employing α-Keto Esters[a]

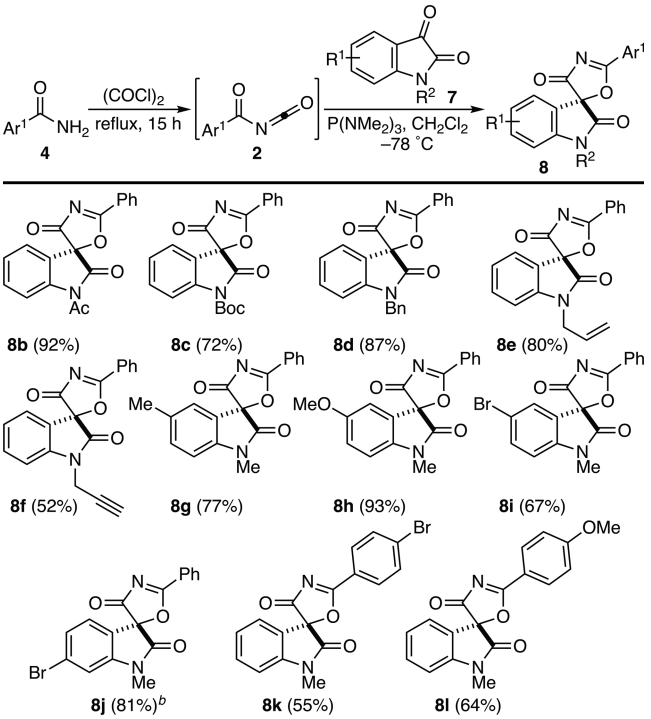


[a]Conditions: **4** (0.24 mmol), **5** (0.20 mmol), $P(NMe_2)_3$ (0.20 mmol), in CH_2Cl_2 (0.2 M).

electron-rich aryl formates, which may be due to isocyanate degradation resulting from slow oxyphosphonium enolate formation.

Extending this strategy to the spirooxindole oxazolone scaffold employing isatin derivatives revealed a broader functional group tolerance than what was observed with the complementary formates (Scheme 5). The formal [4 + 1]-cycloaddition of *N*-acyl isatins with isocyanate **2a** provided spirooxindole oxazolones **8b** and **8c** in 92% and 72% yields respectively, along with *N*-benzyl, -allyl, and -propargyl

Scheme 5. Construction of Spirooxazolone Oxindoles[a]



[a]Conditions: **4** (0.24 mmol), **7** (0.20 mmol), $P(NMe_2)_3$ (0.20 mmol), in CH_2Cl_2 (0.2 M). [b]Isolated as a mixture with *N*,*N*′-carbonyldibenzamide in a 5:1 ratio; see Supporting Information.

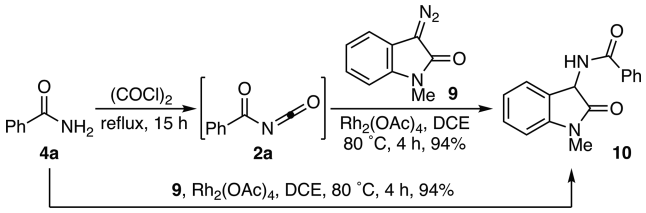
DOI: 10.1021/acs.orglett.8b00656
Org. Lett. 2018, 20, 2315−2319

oxazolones **8d–f** produced in comparable yields. Interestingly, unlike their aryl formate counterparts, the presence of electron-donating groups at the C5 position of *N*-methyl isatin did not hinder oxazolone formation as evidenced by the excellent yields observed in the assembly of **8g** and **8h**. The presence of a bromide at C5 or C6 led to comparable yields of oxazolones **8i** and **8j** in 67% and 81%, respectively. These results seem to indicate that the reactivity of isatins is more impervious to electronic perturbations relative to the corresponding aryl formates.

As we observed in the formate-derived series of oxazolones, cycloadducts were obtained in generally good yields in the formal [4 + 1]-cycloaddition regardless of electron-donating or -withdrawing groups on the aroyl isocyanate. For example, electron-rich and electron-deficient benzamides provided oxazolones **8k** and **8l** in 55% and 64% yields, respectively. It is worth noting that while benzamide *meta*- and *para*-substitution did not significantly hinder the cycloaddition event, *ortho*-substitution led to trace oxazolone formation, presumably due to increased steric encumbrance in either the isocyanate addition or cyclization steps.

Based on our previous work on the development of formal [4 + 1]-cycloadditions employing diazo compounds as C1 synthons, we sought to evaluate the utility of these versatile reagents in the presence of a Rh(II) catalyst toward enabling oxazolone construction.[13] However, we discovered that despite the biphilic similarities of oxyphosphonium enolates and metallocarbenes, these presumptive reaction intermediates led to significantly different outcomes when exposed to aroyl isocyanates. Treatment of aroyl isocyanate **2a**, derived from benzamide (**4a**), with diazooxindole **9** in the presence of 5 mol % $Rh_2(OAc)_4$ failed to provide spirooxindole **8a**, but instead led to formation of 3-amido oxindole **10** in 94% yield (Scheme 6).

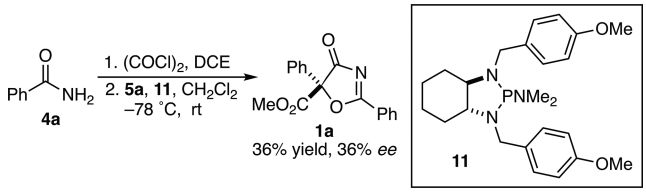
Scheme 6. Amidation of Diazooxindoles



Exposure of **4a** directly to diazooxindole **9** under comparable reaction conditions likewise provided oxindole **10**. While speculative at this stage, a mechanism that involves reversion of isocyanate **2a** to amide **4a**, mediated by residual HCl that is generated upon conversion to the corresponding isocyanate, may rationalize formation of oxindole **10**. Support for this hypothesis was obtained from the observation that vigorous extrusion of HCl from the conversion of **4a** to **2a**, by placing the crude reaction mixture under reduced pressure for 2 h, led to dimerization of diazooxindole **9** and degradation of **2a** in the presence of $Rh_2(OAc)_4$.

In an effort to gain insight into the participation of PL_3 throughout the course of heterocycle formation, we chose to evaluate the potential for optical enrichment of the corresponding C5-disubstituted oxazolone through the use of a chiral trivalent phosphorus reagent. The enantioselective assembly of fully substituted carbon centers remains a nontrivial endeavor in synthesis, and optically enriched oxazolones are synthetically viable precursors to α-hydroxy carboxylic acid derivatives. In 2010, Radosevich first reported the use of stoichiometric chiral phosphoramine **11** in the enantioselective construction of α-hydroxy and α-amino esters proceeding via a Kukhtin–Ramirez-like redox condensation.[14] Although interest in redox phosphorus-catalyzed reactions has increased in recent years, identifying conditions to facilitate catalyst turnover that are compatible with electrophilic functionality present is often an impediment to the development of these methods. However, we anticipated gaining valuable mechanistic insight into oxazolone formation through the use of a stoichiometric chiral phosphoramine. Thus, conversion of benzamide **4a** to the corresponding aroyl isocyanate followed by treatment with formate **5a** and phosphoramine **11** provided oxazolone **1a** in 36% yield and 36% *ee* (Scheme 7). The relatively low yield of

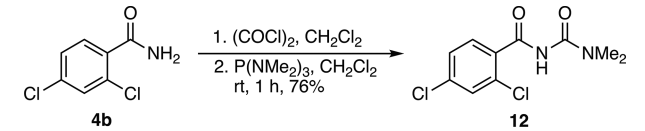
Scheme 7. Stereoinduction with a Chiral Phosphorus Reagent



1a in comparison to those described in Schemes 4 and 5 illustrates the delicate balance between the phosphorus ligation structure and product yield commensurate with our comparison of $P(OMe)_3$ and $P(NMe_2)_3$ (Scheme 3). Despite the low yield and enantiomeric excess, the stereoinduction observed in the assembly of **1a** would indicate that the phosphoramine was present in the enantiodetermining step, leading to oxazolone formation.

A series of control experiments provided additional mechanistic evidence of this $P(NMe_2)_3$-mediated, formal [4 + 1]-cycloaddition approach toward oxazolone construction. For example, when $P(NMe_2)_3$ was omitted from the addition of α-ketoester **5a** to isocyanate **2a**, reversion to benzamide **4a** and quantitative recovery of **5a** were observed. Interestingly, when benzamide **4b** was treated with oxalyl chloride followed by the addition of $P(NMe_2)_3$ at room temperature in the absence of either an aryl formate or isatin derivative, *N*-acyl urea **12** was obtained in 76% yield (Scheme 8). The structure of **12** was

Scheme 8. Ligand Transfer from $P(NMe_2)_3$

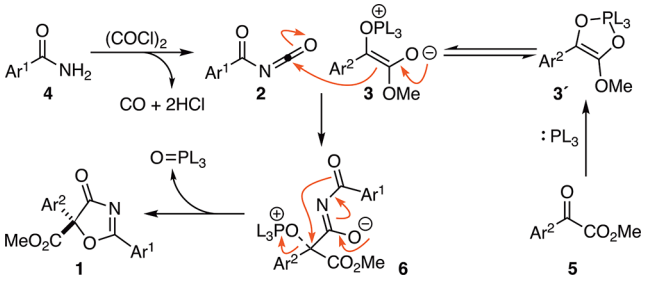


verified by X-ray crystallography and represents a rather unusual ligand transfer event from $P(NMe_2)_3$ to the corresponding aroyl isocyanate. This result, when coupled with the absence of comparable *N*-acyl urea formation when a formate or isatin derivative is present, would seem to indicate that the addition of $P(NMe_2)_3$ to the 1,2-dicarbonyl component is kinetically favored despite the inherent electrophilicity of isocyanates.

Based on our current and previous findings, and in consideration of those reported by Radosevich, Ramirez, and others, a possible mechanism for oxazolone formation is illustrated in Scheme 9. Addition of $P(NMe_2)_3$ to α-ketoester **5**

DOI: 10.1021/acs.orglett.8b00656
Org. Lett. 2018, 20, 2315–2319

Scheme 9. Possible Reaction Mechanism



establishes an equilibrium between dioxaphospholene **3′** and oxyphosphonium enolate **3**. Conversion of amide **4** to aroyl isocyanate **2** employing $(COCl_2)_2$ sets the stage for the addition of **3** to generate oxyphosphonium **6**. Subsequent ring closure via displacement of $O{=}P(NMe_2)_3$ by the imide anion ultimately provides oxazolone **1**. While dissociation of the phosphoramide generates a stabilized, quaternary carbocation, the formation of optically enriched oxazolone **1a** employing **11** suggests the presence of phosphoramide in the transition state of ring closure from **6** to **1**. However, the modest level of enantiomeric excess observed would indicate the possibility of competing associative and dissociative mechanisms.

In conclusion, we have developed a formal trivalent phosphorus-mediated [4 + 1]-cycloaddition strategy for the assembly of C5-disubstituted oxazolones employing aroyl isocyanates as 1,4-dipoles and α-aryl 1,2-dicarbonyls as C1 synthons. Employing α-ketoesters and isatins provided the corresponding formate-derived and spirooxindole oxazolones in good to excellent yields, respectively. The optimized reaction conditions proved exceptionally mild and amenable to scale up. Studies aimed at exploiting this formal [4 + 1]-cycloaddition approach to construct heterocyclic motifs of pharmaceutical and materials significance are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00656.

Experimental procedures, spectroscopic data, and crystallographic data (PDF)

Accession Codes

CCDC 1814365 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CAREER CHE-1056242 and 1665440). We thank Kevin X. Rodriguez and Dr. Allen G. Oliver at the University of Notre Dame for assistance in collecting X-ray crystallographic data.

■ REFERENCES

(1) (a) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611. (b) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952.

(2) (a) Sutin, L.; Andersson, S.; Bergquist, L.; Castro, V. M.; Danielsson, E.; James, S.; Henriksson, M.; Johansson, L.; Kaiser, C.; Flyren, K.; Williams, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4837. (b) Lee, C. M.; Plotnikoff, N. P. *J. Med. Chem.* **1976**, *19*, 731. (c) Dolente, C.; Fasching, B.; Runtz-Schmitt, V.; Schnider, P. *Spiro-Oxazolones*. Patent CA2929488 A1, August 27, 2015. (d) Banerjee, R. G.; Gupta, R. C.; Tuli, D.; Rode, M.; Suthar, B.; Umrani, D.; Pathak, P.; Choksi, T.; Chaudhary, A. *Thiazolinones and oxazolinones and their use as PTP1B inhibitors*. Patent WO2007032028 A1, March 22, 2007.

(3) (a) Shue, Y. K. *Tetrahedron Lett.* **1996**, *37*, 6447. (b) Schiff, P. L. *Am. J. Pharm. Educ.* **2006**, *70*, 98.

(4) (a) Trost, B. M.; Hirano, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6480. (b) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286. (c) Badiola, E.; Fiser, B.; Gomez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; Garcia, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869. (d) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944.

(5) (a) Zhu, G.; Yang, J.; Bao, G.; Zhang, M.; Li, J.; Li, Y.; Sun, W.; Hong, L.; Wang, R. *Chem. Commun.* **2016**, *52*, 7882. (b) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7523. (c) Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696. (d) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944. (e) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358. (f) Morita, A.; Misaki, T.; Sugimura, T. *Tetrahedron Lett.* **2015**, *56*, 264. (g) Morita, A.; Misaki, T.; Sugimura, T. *Chem. Lett.* **2014**, *43*, 1826. (h) Liu, X.; Zhang, J.; Ma, S.; Ma, Y.; Wang, R. *Chem. Commun.* **2014**, *50*, 15714. (i) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377. (j) Wei, Y.; Liu, Z.; Wu, X.; Fei, J.; Gu, X.; Yuan, X.; Ye, J. *Chem. - Eur. J.* **2015**, *21*, 18921.

(6) (a) Ketcha, D. M.; Abou-Gharbia, M.; Smith, F. X.; Swern, D. *Tetrahedron Lett.* **1983**, *24*, 2811. (b) Abou-Gharbia, M.; Ketcha, D. M.; Zacharias, D. E.; Swern, D. *J. Org. Chem.* **1985**, *50*, 2224.

(7) (a) Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *74*, 8381. (b) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

(8) (a) Ramirez, F.; Desai, N. B.; Ramanathan, N. *Tetrahedron Lett.* **1963**, *4*, 323. (b) Ramirez, F.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 3030. (c) Ramirez, F.; Telefus, C. D.; Prasad, V. A. V. *Tetrahedron* **1975**, *31*, 2007. (d) Ramirez, F.; Telefus, C. D. *J. Org. Chem.* **1969**, *34*, 376.

(9) (a) Zhao, W.; Fink, D. M.; Labutta, C. A.; Radosevich, A. T. *Org. Lett.* **2013**, *15*, 3090. (b) Wang, S. R.; Radosevich, A. T. *Org. Lett.* **2015**, *17*, 3810. (c) Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10605. (d) Guo, H. C.; Xu, Q. H.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318. (e) Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radosevich, A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6839. (f) Zhao, W.; Yan, P. K.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 616. (g) Zhao, W.; Radosevich, A. T. *Org. Synth.* **2015**, *92*, 267. (h) Wang, S. R.; Radosevich, A. T. *Org. Lett.* **2013**, *15*, 1926.

(10) (a) Zhou, R.; Zhang, K.; Han, L.; Chen, Y. S.; Li, R. F.; He, Z. J. *Chem. - Eur. J.* **2016**, *22*, 5883. (b) Zhou, R.; Zhang, K.; Chen, Y. S.; Meng, Q.; Liu, Y. Y.; Li, R. F.; He, Z. J. *Chem. Commun.* **2015**, *51*, 14663. (c) Zhan, G.; Shi, M. L.; He, Q.; Du, W.; Chen, Y. C. *Org. Lett.* **2015**, *17*, 4750. (d) Xu, S. L.; Zhou, L. L.; Ma, R. Q.; Song, H. B.; He,

DOI: 10.1021/acs.orglett.8b00656
Org. Lett. 2018, 20, 2315−2319

Z. J. *Org. Lett.* **2010**, *12*, 544. (e) Xu, S. L.; Chen, R. S.; He, Z. J. *J. Org. Chem.* **2011**, *76*, 7528. (f) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem. - Eur. J.* **2009**, *15*, 8698. (g) Tian, J.; Zhou, R.; Sun, H.; Song, H.; He, Z. *J. Org. Chem.* **2011**, *76*, 2374. (h) Zhou, R.; Wang, J.; Song, H.; He, Z. *Org. Lett.* **2011**, *13*, 580.

(11) (a) Wilson, E. E.; Rodriguez, K. X.; Ashfeld, B. L. *Tetrahedron* **2015**, *71*, 5765. (b) Rodriguez, K. X.; Vail, J. D.; Ashfeld, B. L. *Org. Lett.* **2016**, *18*, 4514.

(12) (a) Osman, F. H.; El-Samahy, F. A. *Chem. Rev.* **2002**, *102*, 629. (b) Mark, V. *J. Am. Chem. Soc.* **1963**, *85*, 1884.

(13) (a) Rodriguez, K. X.; Pilato, T. C.; Ashfeld, B. L. *Chem. Sci.* **2018**, *9*, 3221. (b) Rodriguez, K. X.; Kaltwasser, N.; Toni, T. A.; Ashfeld, B. L. *Org. Lett.* **2017**, *19*, 2482. (c) Meloche, J. L.; Ashfeld, B. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 6604.

(14) Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10605.

DOI: 10.1021/acs.orglett.8b00656
Org. Lett. 2018, 20, 2315−2319