Organic LETTERS

Letter

pubs.acs.org/OrgLett

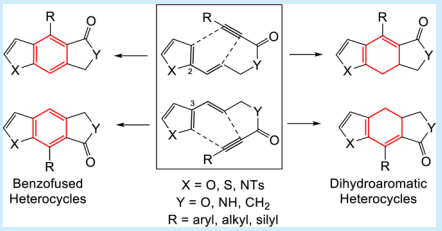
Intramolecular Didehydro-Diels–Alder Reaction for the Synthesis of Benzo- and Dihydrobenzo-Fused Heterocycles

Ashley E. Bober, Justin T. Proto, and Kay M. Brummond*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

ABSTRACT: Using an intramolecular didehydro-Diels–Alder reaction, ene–yne substituted pyrroles, thiophenes, and furans afford functionalized indoles, benzothiophenes, and benzofurans and the corresponding dihydroaromatic products. Product selectivity for the aromatic or dihydroaromatic product is controlled by the reaction conditions, which vary depending upon the substrate.



Benzo- and dihydrobenzo-fused heterocycles are a diverse class of compounds that play important roles in pharmaceuticals, biological probes, and electronic materials.[1] Naturally occurring benzo-fused heterocycles exhibit biological activity in a wide range of therapeutic applications. Indole represents the most prominent of these heterocyclic moieties and is found in many pharmaceuticals and biologically active natural products.[1a,2] Benzothiophenes and benzofurans, although less common, have been the subject of growing attention. For example, colchicine derivative **1** is a lead anticancer compound that displays antiproliferative activity at nanomolar concentrations (Figure 1).[3] Benzothiophene **2** acts as an antithrombotic agent that deactivates plasminogen activator inhibitor-1 during the coagulation process.[4] (−)-Nodulisporic acid C (**3**), an indole derivative, is an orally available antiflea agent used to treat domestic animals.[5] Tetrahydrocarbazole **4** is a promising candidate as a treatment for obesity in rat models.[6]

Rising interest has led to an increased number of synthetic approaches to efficiently generate functionalized benzo-fused heterocycles.[1b,7] Most of these synthetic methods, especially those performed on large scale, begin by constructing the heterocyclic ring from benzene-containing precursors, due to their availability and ease of functionalization.[2a,8] The heterocyclic portion is often formed via condensation reactions,[1a] such as the Fischer indole synthesis, and the conversion of α-haloketones to form benzofurans and benzothiophenes.[1a,9] Modern transition-metal-catalyzed reactions provide alternative conditions for the synthesis of indoles, yet they employ aniline-derived precursors seen in classical reactions that result in the same substitution patterns.[10] In 2014, Njardarson et al. mapped the functionalization patterns of indoles in FDA-approved drugs.[11] Of 17 drugs containing indole scaffolds, 15 contained substitution at the 3-position, and 12 were substituted at the 5-position. In contrast, only one drug incorporated substituents at either the 4- or 7-positions; no drugs were substituted at the 6-position. Structure **5** highlights substitution patterns underrepresented in pharmaceuticals.

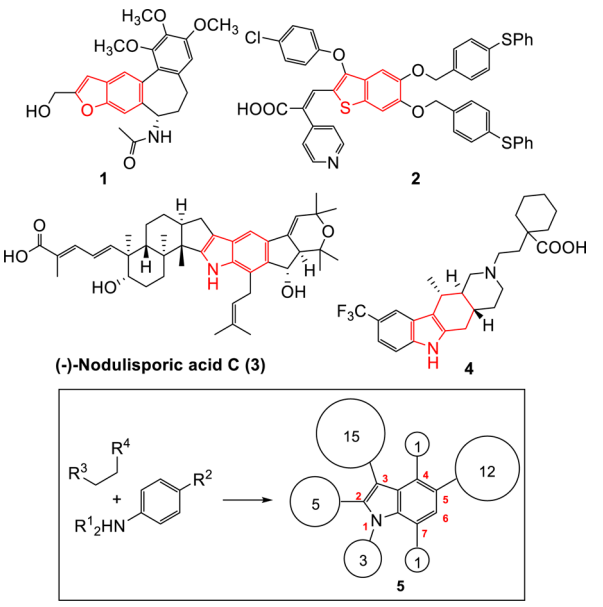


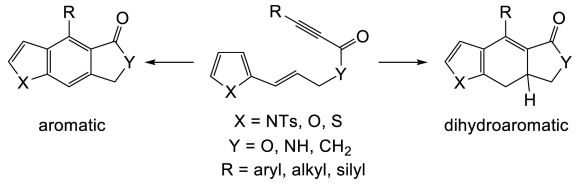
Figure 1. Biologically relevant fused heterocycles. Structure **5** illustrates common substitution patterns in FDA-approved indole drugs, adapted with permission from ref 11. Copyright 2014 American Chemical Society.[11]

The intramolecular didehydro-Diels–Alder (IMDDA) reaction was previously established as a method to efficiently generate naphthalene- and dihydronaphthalene-containing frameworks from the same diene–yne precursors; this divergent method requires only subtle changes to the reaction conditions.[12] Herein, we explore the feasibility of utilizing the IMDDA reaction to prepare benzo-fused heterocycles as an alternate synthetic approach to access more challenging substitution patterns (Scheme 1). The benzo- and dihydro-

Received: January 16, 2017

DOI: 10.1021/acs.orglett.7b00155
Org. Lett. XXXX, XXX, XXX–XXX

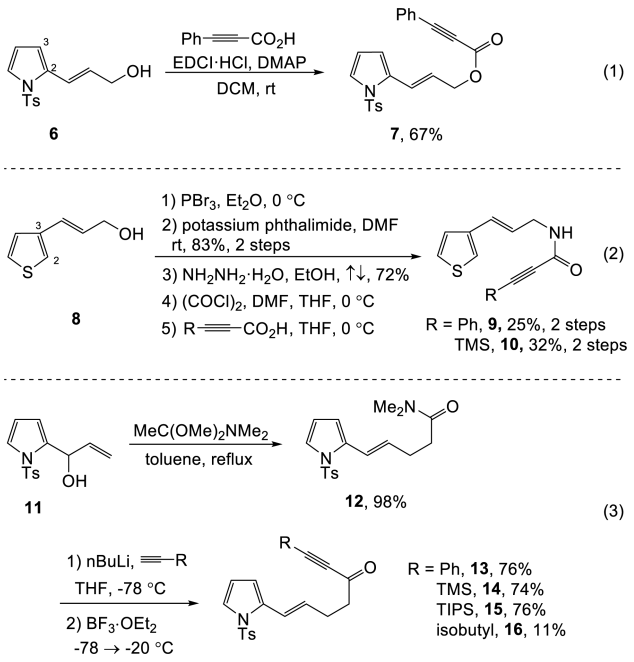
Scheme 1. Heterocyclic Scaffolds via the IMDDA Reaction



fused heterocyclic cores each offer a unique reactivity profiles for subsequent potential applications. The benzo-fused heterocycles show immediate similarity to pharmaceuticals, and the dihydrobenzo-fused heterocycles offer many sites for additional functionality and complexity to be introduced.

To examine the utility of the IMDDA reaction for the preparation of heterocyclic scaffolds, a variety of diene−yne precursors were synthesized. We chose to explore several heterocycles, including thiophene, furan, and pyrrole, as well as a range of tether functionalities. Scheme 2 depicts a representative synthesis of a heterocyclic substrate equipped with an ester-containing tether. Allylic alcohol **6** was prepared via the Wittig reaction of pyrrole-2-carboxaldehyde (98% yield)[13] and subsequent DIBAL reduction (98% yield; see the Supporting Information (SI)). To form the alkynoate tether, the carboxyl-activating reagent EDCI·HCl was used to couple **6** with phenylpropiolic acid to generate 7 in moderate yield (67%; eq 1, Scheme 2). The same process was used to synthesize IMDDA precursors containing tethers at the C3-position of the pyrrole as well as for the thiophene and furan analogues (see the SI).

Scheme 2. Representative Syntheses of IMDDA Precursors

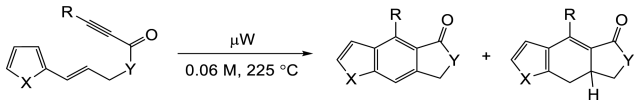


In addition to IMDDA precursors incorporating ester functionality within the diene−yne tether, thiophenes featuring amide moieties were also synthesized via the Gabriel synthesis (eq 2, Scheme 2). Phosphorus tribromide was used to convert allylic alcohol **8** to the corresponding allyl bromide, which was further reacted with potassium phthalimide to deliver the allylic phthalimide in good yield (83%, two steps). Refluxing with hydrazine in ethanol delivered the free amine (72%). To prepare the IMDDA precursor, phenyl- and TMS-substituted propiolic acids were converted to acid chlorides using oxalyl chloride and a catalytic amount of dimethylformamide (DMF). Each acid chloride was added dropwise to the allylamine to provide amides **9** and **10**.

Pyrrole derivatives were also synthesized with incorporation of ketones into the diene−yne tethers (eq 3, Scheme 2). After addition of vinylmagnesium bromide to pyrrole-2-carboxaldehyde,[14] an Eschenmoser−Claisen rearrangement[15] of allyl alcohol **11** afforded dimethyl amide **12** in good yield. Installation of the alkyne moiety was achieved following Trost's procedure.[16] When the alkyne terminus was phenyl-substituted, addition of the alkyne proceeded in 76% yield to generate diene−yne **13**. Comparable yields were observed for TMS and TIPS substitution of the alkyne (**14** and **15**). A poor yield was obtained for the addition of 4-methylpentyne due to the formation of uncharacterized byproducts (**16**, 11% yield).

With the heterocyclic diene−ynes in hand, the IMDDA reaction was tested. Nitrobenzene ($PhNO_2$) as the reaction solvent delivered exclusively the benzothiophene and benzofuran products when ester-containing tethers were installed at the C2-positions (entries 1 and 3, Table 1). On the basis of previous studies of styrenyl substrates, 10% $PhNO_2$ in *o*-dichlorobenzene (*o*-DCB) was sufficient to exclusively generate the aromatic product.[12b] These optimized conditions proved successful when alkynoate tethers were incorporated at the C2-positions of thiophene and furan, affording exclusively aromatic products (entries 2 and 4). When the IMDDA reaction of a pyrrole with an alkynoate tether was conducted using 10% $PhNO_2$, the aromatic product was formed in a 50:50 mixture with the dihydroaromatic product (entry 5). Increasing the concentration of $PhNO_2$ increased the ratio of aromatic to dihydroaromatic product, yet it was not until neat $PhNO_2$ was employed that the aromatic indole was solely formed (entries 5−8). Moving forward, *o*-DCB containing 50% $PhNO_2$ was selected as the medium to generate indoles in IMDDA reactions, as these conditions would minimize the amount of $PhNO_2$ but still allow for enhanced product selectivity (entries 9−10). However, with a TIPS group at the alkyne terminus of the IMDDA precursor, selectivity and yield decreased appreciably (entry 11). The marked decrease in yield is

Table 1. C2-Substituted Aromatic Selectivity



entry	X	Y	R	% $PhNO_2$	time (min)	Ar/DH[a]	% yield[b]
1	S	O	Ph	100[c]	3	100:0	90
2	S	O	TMS	10	20	100:0	86
3	O	O	Ph	100[c]	3	100:0	65
4	O	O	TMS	10	20	100:0	42
5	NTs	O	Ph	10	3	50:50	94
6	NTs	O	Ph	20	3	83:17	94
7	NTs	O	Ph	50	3	97:3	74
8	NTs	O	Ph	100	3	100:0	90
9	NTs	CH_2	Ph	50	3	88:12	99
10	NTs	CH_2	TMS	50	3	93:7	69
11	NTs	CH_2	TIPS	50	10	78:22	41

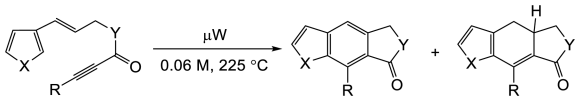
[a] ^{1}H NMR ratios [b] Isolated yield, 0.06−0.13 mmol. [c] Lower conc. not tested.

DOI: 10.1021/acs.orglett.7b00155
Org. Lett. XXXX, XXX, XXX−XXX

attributed to steric interactions between the pyrrole and the isopropyl groups on silicon.

Conditions to provide aromatic product selectivity were also explored for heterocycles with tethers at the C3 position. Thiophene substrates containing ester and amide tethers showed high selectivity for the aromatic products when 10% $PhNO_2$ in *o*-DCB was employed as the reaction solvent (entries 1−5, Table 2). Neat $PhNO_2$ delivered the benzofuran product exclusively in

Table 2. C3-Substituted Aromatic Selectivity



entry	X	Y	R	% $PhNO_2$	time (min)	Ar/DH[a]	% yield[b]
1	S	O	Ph	10	20	96:4	86
2	S	O	TMS	10	20	99:1	71
3	S	O	CH_2Cy	10	80	99:1	71
4	S	NH	Ph	10	30	95:5	82
5	S	NH	TMS	10	30	99:1	74
6	O	O	Ph	100[c]	3	100:0	78
7	NTs	O	Ph	50	5	4:96[d]	57[e]
8	NTs	CH_2	Ph	100	5	81:19	57[e]

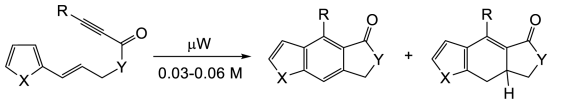
[a]^{1}H NMR ratios. [b]Isolated yield, 0.05−0.11 mmol. [c]Lower conc. not tested. [d]Anomalous result under investigation. [e]Decomposition by TLC.

the reaction of a precursor featuring an ester-containing tether (entry 6). When a pyrrole precursor with an ester-containing tether was reacted in 50% $PhNO_2$, only trace aromatic product was detected by ^{1}H NMR (entry 7). $PhNO_2$ provided the aromatic product in an 81:19 ratio with the dihydroaromatic product for the reaction of a pyrrole precursor with an alkynone tether (entry 8). Significant decomposition was observed by TLC in these cases (entries 7−8).

Reaction in DMF provided dihydroaromatic products with high selectivity for phenyl-substituted alkynes of C2-substituted thiophene and furan systems (entries 1 and 3, Table 3). The dihydroindole lactone product was generated with good selectivity at higher concentrations and temperatures as low as 120 °C (entry 5). For pyrroles with alkynone tethers, high concentrations of the substrate in DMF provided less selectivity, resulting in an 11:89 ratio of the aromatic to dihydroaromatic products (entry 6). Reaction of the same substrate in *o*-DCB at higher temperature and lower concentration afforded an 8:92 ratio of products in excellent yield (99%, entry 7). DCE, although similar in polarity and easier to remove than *o*-DCB, did not deliver the same selectivity for the dihydroaromatic product (entry 8). Reaction in DMF at higher concentration gave the aromatic product in a 60:40 ratio with its dihydroaromatic counterpart for pyrrole featuring a TMS-substituted alkynone tether (entry 9). Changing the solvent to DCE and lowering the reaction temperature yielded exclusively the dihydroindole product (entry 10). Increasing reaction concentration led to decreased selectivity (entry 11). TIPS substitution at the alkyne terminus decreased the reaction rate significantly as well as the selectivity and yield (entry 12).

The dihydroindole examples featuring ketone tethers slowly oxidized to the fully aromatic indole products under air (entries 6−11, Table 3; see the SI). Spontaneous oxidation was not observed for other dihydroaromatic products. However, a dihydroindole with a lactone tether and phenyl substitution

Table 3. C2-Substituted Dihydroaromatic Selectivity



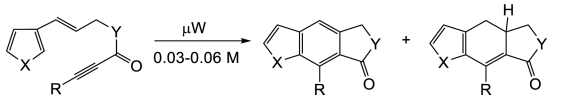
entry	X	Y	R	solvent	*t* (°C)	time (min)	Ar: DH[a]	% yield[b]
1	S	O	Ph	DMF	225	3	3:97	58
2	S	O	TMS	DMF	225	3	21:79	ND
3	O	O	Ph	DMF	225	3	5:95	41
4	O	O	TMS	DMF	225	15	-	-[d]
5	NTs	O	Ph	DMF[c]	120	10	5:95	86
6	NTs	CH_2	Ph	DMF[c]	180	5	11:89	85
7	NTs	CH_2	Ph	o-DCB	225	3	8:92	99
8	NTs	CH_2	Ph	DCE	120	180	33:67	72
9	NTs	CH_2	TMS	DMF[c]	180	20	60:40	57
10	NTs	CH_2	TMS	DCE	150	120	0:100	76
11	NTs	CH_2	TMS	DCE[c]	150	120	16:84	71
12	NTs	CH_2	TIPS	DCE	150	240	38:62	10[e]

[a]^{1}H NMR ratios. [b]Isolated yield, 0.06−0.09 mmol. [c]Reaction conc. 0.10−0.12 M. [d]No products detected, only decomposition. [e]63% recovery SM.

was successfully oxidized to the corresponding indole via manganese(IV) oxide (see the SI).[17]

Conditions to provide the dihydroaromatic product selectively were also explored for heterocycles with tethers at the C3-position. The thiophene precursor containing an alkynoate tether yielded the dihydroaromatic product selectively in DMF at 180 °C (entry 1, Table 4). Reaction of a TMS-substituted thiophene precursor in DMF at 225 °C produced a 12:88 ratio of the aromatic to dihydroaromatic products in 48% yield; however, the TMS group was cleaved in situ (entry 2). Alkyl substitution of the alkyne terminus positively impacted selectivity, which was increased to 7:93 in favor of the dihydroaromatic product (entry

Table 4. C3-Substitued Dihydroaromatic Selectivity



entry	X	Y	R	solvent	*t* (°C)	time (min)	Ar: DH[a]	% yield[b]
1	S	O	Ph	DMF[c]	180	10	4:96	>99[d]
2	S	O	TMS	DMF	225	3	12:88	48[e]
3	S	O	CH_2Cy	DMF	225	15	7:93	71
4	S	NH	Ph	DMF	180	90	34:66	ND
5	S	NH	TMS	DMF	180	90	38:62	26[f]
6	O	O	Ph	DMF	225	3	12:88	36
7	NTs	O	Ph	DMF[c]	150	50	16[g]:84	37
8	NTs	O	Ph	*o*-DCB[c]	180	45	0:100	49
9	NTs	O	Ph	*o*-DCB	225	3	0:100	75
10	NTs	CH_2	Ph	DMF[c]	180	40	0:100	95

[a]^{1}H NMR ratios. [b]Isolated yield, 0.03−0.1 mmol. [c]Reaction conc. 0.10−0.12 M. [d]Crude yield. [e]TMS cleaved. [f]Decomposition by TLC. [g]Not isolated.

DOI: 10.1021/acs.orglett.7b00155
Org. Lett. XXXX, XXX, XXX−XXX

3). Reaction of the substrate with an amide tether and Ph substitution at the alkyne terminus gave a 34:66 ratio of aromatic to dihydroaromatic products (entry 4). A TMS-substituted analogue had a comparable product ratio (38:62, entry 5). The reaction of a furanyl alkynoate precursor in DMF achieved fair selectivity for the dihydroaromatic product in low yield (entry 6). Mild selectivity for the dihydroaromatic product and low yield was observed for the reaction of a pyrrole alkynoate precursor in DMF at 150 °C (entry 7). Changing the solvent to *o*-DCB and raising the temperature to 180 °C gave complete selectivity for the dihydroindole and a slightly improved yield (entry 8). Decreasing the concentration to 0.03 M and raising the reaction temperature to 225 °C maintained exclusive selectivity for the dihydroindole while significantly improving the yield to 75% (entry 9). High reaction temperatures were required to drive the reaction to completion and circumvent decomposition of the starting material. In contrast, reaction of a pyrrole precursor containing an alkynone tether afforded exclusively the dihydroindole in 95% yield (entry 10).

Using the conditions described within, the IMDDA reaction provides a useful alternative route to thiophene-yl and pyrrolyl systems. While the product selectivities for the furanyl heterocycles are high, the yields for these transformations are lower than for the thiophene-yl and pyrrolyl systems. For most cases examined, product selectivity is controlled by the IMDDA reaction conditions, as predicted by previous studies in our laboratory on naphthalenes and dihydronaphthalenes. However, the heterocyclic substrates also play a role in product selectivities, showing different propensities to form the dihydroaromatic and aromatic products as compared to the corresponding styrenyl substrates.[12,18] The thiophene substrates give better selectivity for the aromatic product than the pyrrole compounds. On the other hand, the pyrrole precursors selectively deliver dihydroaromatic products at relatively low temperatures and in higher yields. Yields for C2-substituted IMDDA reactions are marginally higher than for the analogous C3-substituted heterocycles, although the reaction times are consistent where comparable. The substituent on the terminus of the alkyne markedly affects the yield of the IMDDA reaction, with phenyl-substituted alkynes affording higher yields than the silyl- or alkyl-substituted examples.

Experiments to further investigate the heterocyclic IMDDA reaction mechanism are ongoing. In addition, functionalization reactions of these heterocyclic scaffolds are being explored to generate the complexity observed in natural products and pharmaceuticals. Future directions also include the development of enantioselective reaction conditions for dihydroaromatic product formation. The IMDDA reaction of heterocyclic diene−ynes is a complementary and efficient route to functionalized benzo- and dihydrobenzo-fused heterocycles with less prevalent substitution patterns. Extensive reaction screening experiments were used to investigate product selectivity and establish optimized conditions for selective generation of the aromatic and dihydroaromatic scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00155.

Experimental procedures and characterization data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kbrummon@pitt.edu.

ORCID

Kay M. Brummond: 0000-0003-3595-6806

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the NSF (CHE-1465032) for financial support.

■ REFERENCES

(1) (a) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442−495. (b) Wu, B.; Yoshikai, N. *Org. Biomol. Chem.* **2016**, *14*, 5402−5416.

(2) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629−661.

(3) Voitovich, Y. V.; Shegravina, E. S.; Sitnikov, N. S.; Faerman, V. I.; Fokin, V. V.; Schmalz, H.-G.; Combes, S.; Allegro, D.; Barbier, P.; Beletskaya, I. P.; Svirshchevskaya, E. V.; Fedorov, A. Y. *J. Med. Chem.* **2015**, *58*, 692−704.

(4) De Nanteuil, G.; Lila-Ambroise, C.; Rupin, A.; Vallez, M.-O.; Verbeuren, T. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1705−1708.

(5) (a) Zou, Y.; Melvin, J. E.; Gonzales, S. S.; Spafford, M. J.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 7095−7098. (b) Bills, G. F.; González-Menéndez, V.; Martín, J.; Platas, G.; Fournier, J.; Persoh, D.; Stadler, M. *PLoS One* **2012**, *7*, e46687.

(6) Mihalic, J. T.; Fan, P.; Chen, X.; Chen, X.; Fu, Y.; Motani, A.; Liang, L.; Lindstrom, M.; Tang, L.; Chen, J.-L.; Jaen, J.; Dai, K.; Li, L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3781−3785.

(7) (a) Lima, H. M.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2012**, *14*, 2274−2277. (b) Chuang, K. V.; Kieffer, M. E.; Reisman, S. E. *Org. Lett.* **2016**, *18*, 4750−4753. (c) Wang, T.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 13870−13873.

(8) (a) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195−7210. (b) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29−41. (c) Guo, T.; Jiang, Q.; Yu, Z. *Org. Chem. Front.* **2015**, *2*, 1361−1365.

(9) Ashcroft, C. P.; Hellier, P.; Pettman, A.; Watkinson, S. *Org. Process Res. Dev.* **2011**, *15*, 98−103.

(10) Guo, T.; Huang, F.; Yu, L.; Yu, Z. *Tetrahedron Lett.* **2015**, *56*, 296−302.

(11) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(12) (a) Kocsis, L. S.; Benedetti, E.; Brummond, K. M. *Org. Lett.* **2012**, *14*, 4430−4433. (b) Kocsis, L. S.; Kagalwala, H. N.; Mutto, S.; Godugu, B.; Bernhard, S.; Tantillo, D. J.; Brummond, K. M. *J. Org. Chem.* **2015**, *80*, 11686−11698.

(13) Peng, H.; Soeller, C.; Travas-Sejdic, J. *Macromolecules* **2007**, *40*, 909−914.

(14) Fujii, M.; Nishiyama, T.; Choshi, T.; Satsuki, N.; Fujiwaki, T.; Abe, T.; Ishikura, M.; Hibino, S. *Tetrahedron* **2014**, *70*, 1805−1810.

(15) (a) Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B. *Can. J. Chem.* **1979**, *57*, 1746−9. (b) Singh, N.; Pulukuri, K. K.; Chakraborty, T. K. *Tetrahedron* **2015**, *71*, 4608−4615. (c) Yoshida, M.; Kasai, T.; Mizuguchi, T.; Namba, K. *Synlett* **2014**, *25*, 1160−1162. (d) Yoshida, M.; Shoji, Y.; Shishido, K. *Tetrahedron* **2010**, *66*, 5053−5058. (e) Honda, Y.; Morita, E.; Ohshiro, K.; Tsuchihashi, G.-i. *Chem. Lett.* **1988**, *17*, 21−24. (f) Davidson, A. H.; Wallace, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1759−1760.

(16) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625−6633.

(17) Míšek, J.; Teplý, F.; Stará, I. G.; Tichý, M.; Šaman, D.; Císařová, I.; Vojtíšek, P.; Starý, I. *Angew. Chem., Int. Ed.* **2008**, *47*, 3188−3191.

(18) Brummond, K. M.; Kocsis, L. S. *Acc. Chem. Res.* **2015**, *48*, 2320−2329.

DOI: 10.1021/acs.orglett.7b00155
Org. Lett. XXXX, XXX, XXX−XXX