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Rapid Assembly of Protoilludane Skeleton through Tandem Catalysis: Total Synthesis of Paesslerin A and Its Structural Revision

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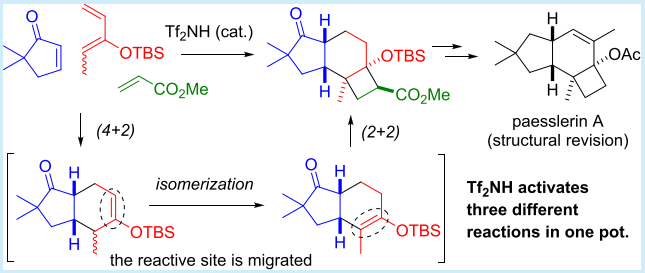
Supporting Information

ABSTRACT: A multicomponent domino reaction involving three mechanistically distinct Tf_2NH-catalyzed reactions was developed. The reaction cascade enables the assembly of a skewed 5/6/4 tricyclic motif with migration of the reactive site with the assistance of a catalyst. The tricyclic product was used to achieve the first total synthesis of cytotoxic paesslerin A by regioselective C−H insertion of the sulfonyl carbenoid and base-promoted olefin isomerization. Our results led to the revision of the originally proposed tricyclic structure of paesslerin A.



A variety of organic substances, including structurally complex molecules, are found in Nature. Their biosynthesis occurs within living organisms and is generally catalyzed by enzymes. In some cases, enzyme complexes such as fatty acid, polyketide, and polypeptide synthases catalyze more than two mechanistically distinct reactions sequentially.[1] Therefore, high-order molecular structures can be efficiently formed from simpler materials, accompanied by the formation of several covalent bonds and stereogenic centers. In synthetic chemistry, domino reactions[2] and related processes such as multicomponent[3] and one-pot reactions[4] are attractive as complementary methods to biosynthesis, because they can be used to build structurally complex molecules in one operation. Major advantages of such procedures include operational simplicity, time and cost savings, atom economy, environmental benignancy, and applicability to diversity-oriented synthesis and combinatorial chemistry. Their catalytic variants have also been investigated to identify more-efficient processes. In typical domino and/or multicomponent reactions, a potential bond-forming reactive site (functionality) of an intermediate, which is produced in the preceding step, is directly used in the subsequent bond-forming reaction (Figure 1, path a). The chemoselectivity, regioselectivity, and stereoselectivity arising during the reaction cascade to the product is usually defined by the nature of the substrates. However, if the reactive site moves to another position during the domino reaction, with the assistance of a catalyst, the construction of diverse and complex structures is possible (Figure 1, path b). Recently, tandem catalysis has attracted much interest as an efficient synthetic strategy.[5] The term "tandem catalysis" is defined as one or more compatible catalysts that independently promote two or more mechanistically distinct reactions in a cascade. We envisioned that a tandem catalysis strategy in which bond-forming reaction(s) and rearrangement of the reactive functional group were sequentially activated by the same catalyst would achieve the difficult goal: a rapid assembly of more-complex molecules in one operation.

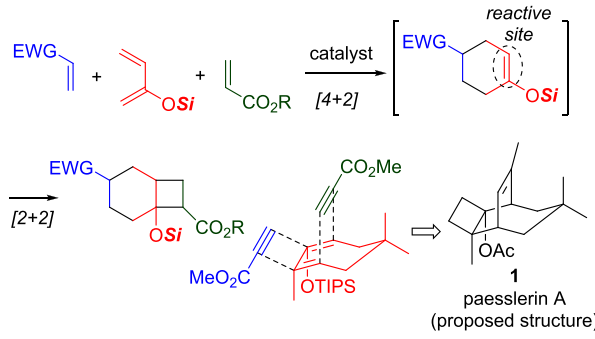


Figure 1. Examples for a typical domino bond-formation reaction (path a) and for domino reaction with migration of a reactive site during the bond-formation reaction cascade (path b).

We reported a catalytic multicomponent cycloaddition, a domino [4 + 2]−[2 + 2] cycloaddition, starting with 2-siloxybutadiene and two molecules of an α,β-unsaturated ester (see Figure 2).[6]

In the reaction cascade, the formation of new C−C bonds in the second [2 + 2] cycloaddition stage occurs directly at the reactive silyl enol ether, which is generated by the first [4 + 2] cycloaddition. By using this reaction as a key step, a rapid synthesis of the proposed structure of paesslerin A (**1**), which was isolated from the sub-Atrantic soft coral *Alcyonium*

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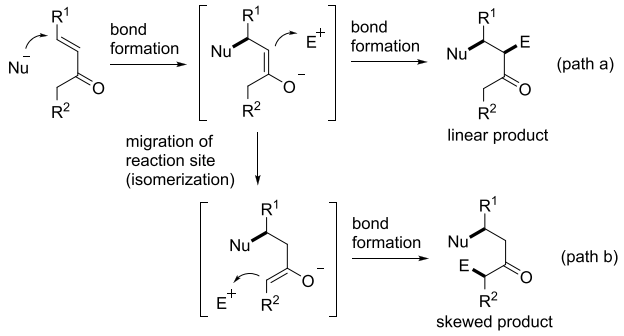


Figure 2. Catalytic domino [4 + 2]−[2 + 2] cycloaddition for the synthesis of the originally reported structure of paesslerin A.

paessleri,[7] and which displays antitumor activity against human cancer cell lines, was accomplished.[6a] However, the spectroscopic data of synthetic **1** were not consistent with those of the natural compound. Based on reassignment of one-dimensional (1D) and two-dimensional (2D) NMR signals of the isolated natural product, it was suspected that the possible structure of the natural paessrerin A would be an acetyl derivative of protoilludenol (**2b**),[8] whose core skeleton is tricyclo-[6.3.0.0^{2,5}]undecane. The skewed 5/6/4 tricyclic system is found in Nature as the core structure of protoilludane sesquiterpens, which were mainly isolated as fungal metabolites.[9] A variety of oxidized metabolites of protoilludanes and their derivatives have been isolated, and several of these show promising biological activities.[10] It is known that the hydroxy substituent at the 6/4 ring juncture would be important for the biological activity from the structure−activity relationship analysis. Because of the characteristic tricyclic structure of protoilludanes, many researchers have investigated the synthetic studies.[11] Most of these are directed to the synthesis protoilludanes having no hydroxy group at the 6/4 ring juncture. In contrast, the synthetic studies toward protoilludanes with a hydroxy group at the 6/4 ring juncture are rare;[12] the total synthesis was recently accomplished only by Sheidt's group.[12b] We envisaged that the key structure could be constructed in a single operation if the silyl enol ether was isomerized using a tandem catalyst in a multicomponent reaction cascade (Figure 3). Here, we describe a catalytic

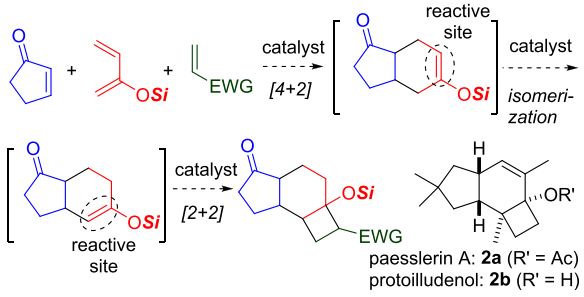
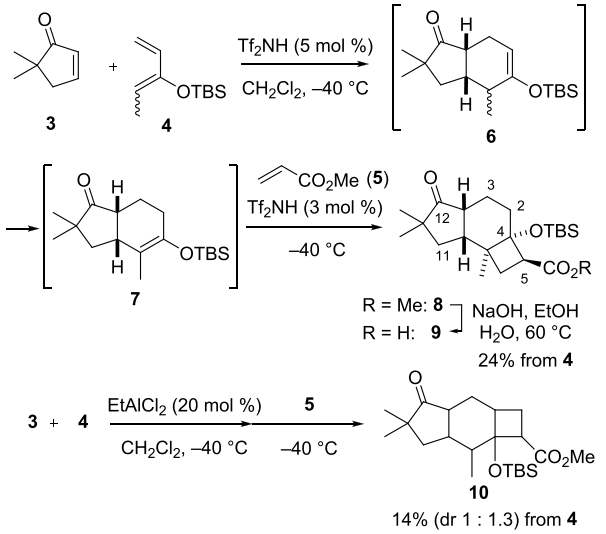


Figure 3. Domino process for production of skewed skeleton for synthesis of newly suggested structure of paesslerin A (**2a**).

three-component reaction consisting of [4 + 2] cycloaddition, isomerization, and [2 + 2] cycloaddition. We also report the first total synthesis of the cytotoxic sesquiterpenoid paesslerin A, and its structural revision.

Recently, we found that isomerization of kinetically favored silyl enol ethers to thermodynamically stable ones occurs smoothly in the presence of Tf_2NH.[13] It has been reported that the same catalyst also activates Diels−Alder type [4 + 2] cycloaddition of enones with 2-siloxydiene[14] and [2 + 2] cycloaddition of silyl enol ethers with acrylate.[15] We chose cyclopentenone **3**,[16] siloxydiene **4**,[17] and methyl acrylate (**5**) as the components for the synthesis of the protoilludane skeleton. A mixture of **3**, **4**, and **5** in CH_2Cl_2 was treated with a catalytic amount of Tf_2NH, which resulted in the production of a complex mixture. The mass spectrum of the crude mixture indicated the formation of three-component adducts. Careful optimization of the reaction conditions showed that a one-pot procedure afforded the desired tricyclo[6.3.0.0^{2,5}]undecanone **8** as the major product (Scheme 1). The reaction of **3** with **4**

Scheme 1. Assembly of Tricyclic Intermediate



(1.1 equiv) in the presence of Tf_2NH (2 mol %) was performed at −40 °C, and then **5** (2.5 equiv) and Tf_2NH (3 mol %) were added at the same temperature, when monitoring via thin-layer chromatography (TLC), showed completion of isomerization of cycloadduct **6** to the thermodynamically favored silyl enol ether **7**. The desired tricyclic adduct **8** was obtained in 34% yield as the major isomer. In the reaction, no regioisomer was observed and a trace amount of diastereomers was detected. It was found that the *E*/*Z* ratio of **4** did not influence the yield and stereoselectivity of **6**. The structure of **8** was determined by X-ray crystallography, after hydrolysis to **9**; **8** had the core structure of protoilludane sesquiterpenes. It is worth noting that the preparation of a multigram quantity of **9** (12 g), which can be easily purified simply by recrystallization, was also successful from **3** (15 g) without isolation of ester **8** (18%−30% overall yield, 23% average). The domino reaction involving isomerization, which affords the skewed 5/6/4 tricyclic adduct **8**, is clearly complementary to the domino reaction with $EtAlCl_2$, which does not activate isomerization of the silyl enol ether. In the presence of $EtAlCl_2$, instead of the formation of the skewed tricycle **8**, linear 5/6/4 tricycle **10** was observed.

A key issue in accomplishing the synthesis of **2** from **9** is the installation of a methyl group at the C(2) position. We expected that either the ketocarbonyl, *tert*-hydroxy, or carboxyl group of **9** would be used as a directing group for functionalization of the inactive C−H bond at the C(2) or C(3) position. Although various direct and indirect C−H

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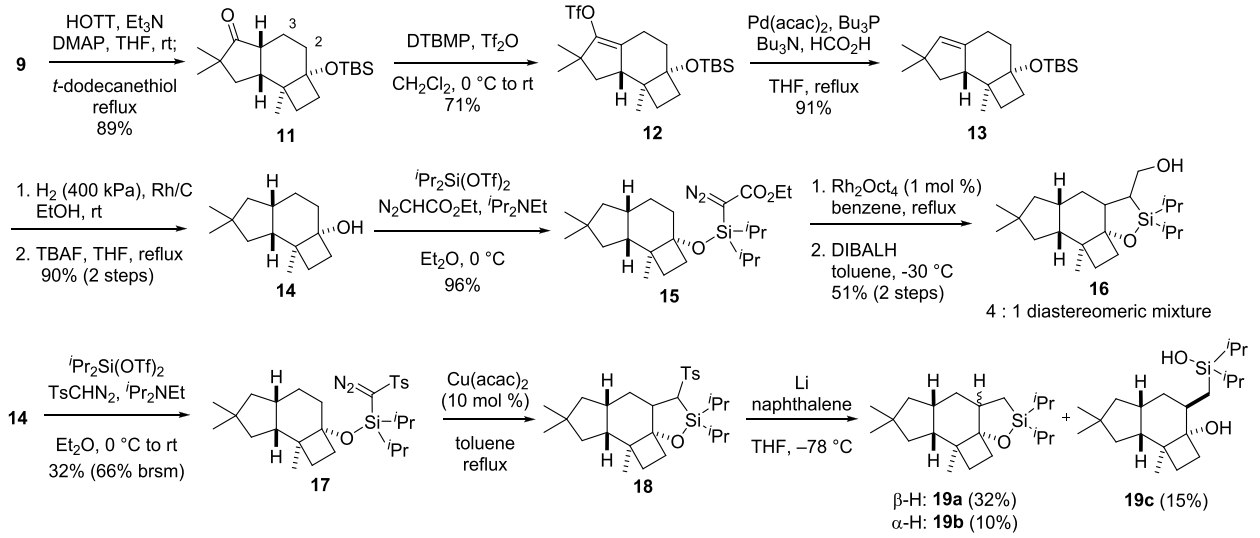
Scheme 2. Introduction of One-Carbon Unit at the C(2) Position[a]

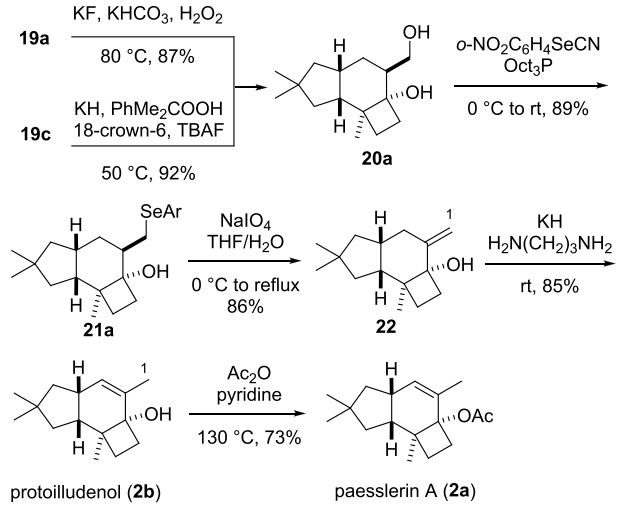


[a]Legend: HOTT, *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate; DTMBP, 2,6-di-*tert*-butyl-4-methylpyridine; and Rh_2Oct_4, dirhodium(II) tetrakis(octanoate).

activation reactions were attempted (see the Supporting Information), decomposition of the fused 6/4 system was observed in many cases, because of the high reactivity of the *tert*-cyclobutanol moiety under acidic, basic, or radical conditions.[18] Finally, we found that an intramolecular carbenoid insertion[19] directed by the *tert*-hydroxy group was promising. The substrate **15** for the carbene insertion was prepared from **9** in six steps, as shown in Scheme 2. Reductive decarboxylation of **9** was performed using a modified Barton's decarboxylative reagent, *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT),[20] to afford **11**. Enol triflation of **11**, followed by hydrogenation, afforded alkene **13**[21] in high yield. After stereoselective reduction of **13**, using a rhodium/carbon catalyst under a high pressure of hydrogen gas (H_2), desilylation of the resulting product provided alcohol **14** in 90% yield (two steps). Installation of the silicon-tethered diazoacetate into **14** was conducted using diisopropylsilyl bis(trifluoromethanesulfonate) and ethyl diazoacetate in the presence of Hünig base, to afford **15** in 96% yield. The C−H insertion reaction of **15** was achieved smoothly by treatment with Rh_2Oct_4, to furnish the tetracyclic ester as a mixture of diastereomers, which was purified after reduction to the corresponding alcohol **16**. The silyl group of **15** not only served as a tether but also masked the hydroxyl group. Once we had successfully introduced two carbon units at the C(2) position, we investigated whether the reaction of diazosulfonate rather than a diazo ester tethered to silicon would lead to one-carbon insertion at the same position. Tosyl diazomethane **17** was prepared from **14** in 32% yield (66%, based on recovered starting material (brsm)) in the same manner as **15**. C−H insertion of diazo tosylate **17**, $Cu(acac)_2$ (where acac = acetylacetonate) was found to be superior to rhodium(II) salts such as Rh_2Oct_4 and $Rh_2(esp)_2$, as a catalyst. Under the optimal conditions, the tetracyclic compound **18** was obtained as an inseparable diastereomeric mixture. After desulfonylation of **18** with lithium naphthalenide, isolable siloxanes **19a** and **19b**, and silanol **19c** were obtained in 32%, 10%, and 15% yields (two steps), respectively. No regioisomer, which could be produced by an insertion reaction into another C−H bond, was detected. The relative configurations were assigned using 2D NMR spectroscopy, and the structure of **19c** was confirmed by X-ray crystallography. It was found that silanol **19c** was mainly formed from **19a** during silica gel column chromatography.

Once we had synthesized the all-carbon motif of protoilludane sesquiterpenes, we focused our attention on the introduction of an *endo* olefin into the six-membered ring as the final stage of the synthesis of **2**, as shown in Scheme 3.

Scheme 3. Final Steps in Total Synthesis of Paesslerin A: Ar in 21a, *o*-Nitrophenyl



Cleavage of the C−Si bond of 1,2-oxasilolane **19a** was achieved via Tamao−Fleming oxidation, providing diol **20a** in 87% yield. Silanol **19c** was also transformed to **20a** in high yield under the modified conditions, using cumene hydroperoxide as an oxidant.[22] Nishizawa−Grieco dehydration of **20a** afforded *exo*-methylene **22** through the formation of selenide **21a**.[23] It is worth noting that the minor diastereomer of 1,2-oxasilolane, **19b**, was converted to **22** by the same reaction sequence (74% yield in three steps). Therefore, all three products obtained in the carbene insertion can be

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converted to **22**. Isomerization of *exo* olefin **22** using acid or transition-metal catalysts was examined, but we only observed recovery or decomposition of the starting material. However, a density functional theory calculation (B3LYP/6-31G*) indicated that the energy level of *exo*-**22** in the ground state is higher than that of *endo*-**2b** (ΔE° = +5.5 kcal/mol). Encouraged by the result, we continued to examine the isomeriazation under basic conditions. We speculated that formation of the allyl anion from **22** would promote isomerization to the *endo* olefin, because the countercation bound to the C(1) atom could be stabilized by chelation with the anionic oxygen atom generated from the *tert*-hydroxyl group. Treatment of **22** with excess KAPA (potassium 3-aminopropylamide),[24] prepared from potassium hydride and 1,3-diaminopropane, successfully promoted isomerization to the *endo* cyclic olefin, to give protoilludenol (**2b**), which was isolated by Nozoe and co-workers from the mycelium of *Fomitopsis insularis*.[8] Finally, acetylation of **2b** with acetic anhydride (as the solvent) in the presence of pyridine rendered **2a** in 73% yield. The physical properties of (±)-**2a** (^{1}H and ^{13}C NMR spectra and low-resolution MS) were identical to those reported for paesslerin A.[7]

In conclusion, a novel multicomponent reaction involving three mechanistically distinct Tf_2NH-catalyzed reactions—[4 + 2] and [2 + 2] cycloadditions, and isomerization—was developed. The reaction cascade enables the assembly of a skewed 5/6/4 tricyclic motif with migration of the reactive site with the assistance of the catalyst. We used this process for rapid construction of the protoilludane skeleton as a key step in the first total synthesis of the racemic protoilludene sesquiterpenes, protoilludenol and paesslerin A, in 17 and 18 overall steps, respectively, from 5,5-dimethyl-2-cyclopentenone. This achievement led to revision of the originally assigned tricyclic structure of paesslerin A. The synthesis also features the regioselective C−H insertion of a silicon-tethered sulfonyl carbenoid and base-promoted isomerization of an *exo* olefin to the *endo* one without decomposition of the unstable *tert*-cyclobutanol moiety.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01089.

Experimental procedures and characterization data for the intermediates (PDF)

Characterization data for the products (PDF)

Accession Codes

CCDC 1906155 and 1906156 contain 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.

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■ REFERENCES

(1) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: Chichester, U.K., 2002.

(2) (a) Tietze, L. F. *Domino Reactions: Concepts for Organic Synthesis*; Wiley−VCH: Weinheim, Germany, 2014. (b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009. (c) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442−524.

(3) (a) Zhu, J.; Wang, Q.; Wang, M. *Multicomponent Reactions in Organic Synthesis*; Wiley−VCH: Weinheim, Germany, 2014. (b) Müller, T. J. J., Ed. *Science of Synthesis: Multicomponent Reactions*, Vols. *1 and 2*; Thieme: Stuttgart, Germany, 2014. (c) Touré, B. G.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439−4486. (d) Villaume, M. T.; Baran, P. S. *Nature* **2014**, *513*, 324−325. (e) Sahn, J. J.; Granger, B. A.; Martin, S. F. *Org. Biomol. Chem.* **2014**, *12*, 7659−7672.

(4) (a) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607. (b) Calder, E. D. D.; Grafton, M. W.; Sutherland, A. *Synlett* **2014**, *25*, 1068−1080.

(5) (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (b) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem. - Eur. J.* **2009**, *15*, 12168−12179. (c) Takasu, K. *Yuki Gosei Kagaku Kyokaishi* **2014**, *72*, 770−780.

(6) (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352−1353. (b) Takasu, K.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2008**, *49*, 4220−4222.

(7) Rodriguez Brasco, M. F.; Seldes, A. M.; Palermo, J. A. *Org. Lett.* **2001**, *3*, 1415−1417.

(8) Nozoe, S.; Kobayashi, H.; Urano, S.; Furukawa, J. *Tetrahedron Lett.* **1977**, *18*, 1381−1384.

(9) Quin, M. B.; Flynn, C. M.; Schmidt-Dannert, C. *Nat. Prod. Rep.* **2014**, *31*, 1449−1473.

(10) Abraham, W. R. *Curr. Med. Chem.* **2001**, *8*, 583−606.

(11) As a review, see: (a) Siengalewicz, P.; Mulzer, J.; Rinner, U. *Eur. J. Org. Chem.* **2011**, *2011*, 7041−7055. As representative examples, see: (b) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747−759. (c) Rychlet Elliott, M.; Dhimane, A.-L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427−3428. (d) Kögl, M.; Brecker, L.; Warrass, R.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9320−9322. (e) Schwartz, B. D.; Matousova, E.; White, R.; Banwell, M. G.; Willis, A. C. A. *Org. Lett.* **2013**, *15*, 1934−1937. (f) Baumann, A. N.; Eisold, M.; Didier, D. *Org. Lett.* **2017**, *19*, 2114−2117.

(12) (a) Pitaval, A.; Leboeuf, D.; Ceccon, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 4580−4583. (b) Hovey, M. T.; Cohen, D. T.; Walden, D. M.; Cheong, P. H.-Y.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 9864−9867.

(13) Inanaga, K.; Ogawa, Y.; Nagamoto, Y.; Daigaku, A.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *Beilstein J. Org. Chem.* **2012**, *8*, 658−661.

(14) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 375−378.

DOI: 10.1021/acs.orglett.9b01089
Org. Lett. XXXX, XXX, XXX−XXX

(15) (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668−3669. (b) Takasu, K. *Synlett* **2009**, *2009*, 1905−1914. (c) Kurahashi, K.; Yamaoka, Y.; Takemoto, Y.; Takasu, K. *React. Chem. Eng.* **2018**, *3*, 626−630.
(16) (a) Agosta, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1971**, *93*, 5513−5520. (b) Cohen, T.; McNamara, K.; Kuzemko, M. A.; Ramig, K.; Landi, J. J., Jr.; Dong, Y. *Tetrahedron* **1993**, *49*, 7931−7942.
(17) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089−2100.
(18) (a) Takasu, K.; Nagao, S.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 1005−1008. (b) Takasu, K.; Nagamoto, Y.; Takemoto, Y. *Chem. - Eur. J.* **2010**, *16*, 8427−8432. (c) Azuma, T.; Takemoto, Y.; Takasu, K. *Chem. Pharm. Bull.* **2011**, *59*, 1190−1193.
(19) Davies, H. M. L.; Dick, A. R. *Top. Curr. Chem.* **2009**, *292*, 303−3145.
(20) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732−5733.
(21) (a) Kablean, S. N.; Marsden, S. P.; Craig, A. M. *Tetrahedron Lett.* **1998**, *39*, 5109−5112. (b) Marsden, S. P.; Pang, W.-K. *Tetrahedron Lett.* **1998**, *39*, 6077−6080.
(22) (a) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044−6046. (b) Ventocilla, C. C.; Woerpel, K. A. *J. Org. Chem.* **2012**, *77*, 3277−3283.
(23) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.
(24) Brown, C. A. *J. Chem. Soc., Chem. Commun.* **1975**, 222−223.

DOI: 10.1021/acs.orglett.9b01089
Org. Lett. XXXX, XXX, XXX−XXX