Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

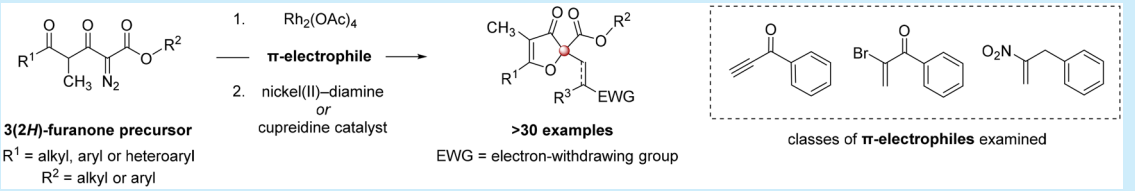
Enantioselective Conjugate Additions of 2-Alkoxycarbonyl-3(2*H*)-furanones

Petra Vojáčková,[†,‡,§] David Chalupa,[†,‡,§] Jozef Prieboj,[†] Marek Nečas,[†] and Jakub Švenda*[,†,‡]

[†]Department of Chemistry, Masaryk University, Brno, 625 00, Czech Republic

[‡]International Clinical Research Center, St. Anne's University Hospital, Brno, 656 91, Czech Republic

Supporting Information



ABSTRACT: Enantioselective conjugate additions of in situ generated 2-alkoxycarbonyl-3(2*H*)-furanones to three distinct types of π-electrophiles (terminal alkynones, α-bromo enones, and α-benzyl nitroalkenes) are reported. Catalysis by a nickel(II)−diamine complex provided alkynone-derived adducts with high enantioselectivity, preferentially as the *Z*-isomers, and completely suppressed the undesired O-alkylation pathway. A cupreidine-based catalyst enabled extension of the enantioselective conjugate additions to α-bromo enones and α-benzyl nitroalkenes. The densely functionalized adducts that result are useful precursors to synthetic analogs of spirocyclic natural products pseurotins.

3(2*H*)-Furanone is found as a substructure of numerous bioactive natural products including pseurotin A (**1**),[1] hyperolactone C (**2**),[2] trachyspic acid (**3**),[3] jatrophone (**4**),[4] and eremantholide A (**5**)[5] (Figure 1), where the 3(2*H*)-furanone ring is most often polysubstituted and carries a quaternary stereocenter at the C2 position (furan numbering). Benzo-3(2*H*)-furanone is a closely related ring-fused analog and, though less frequent in natural products, can be found in the FDA-approved antifungal agent griseofulvin (**6**)[6] (Figure 1).

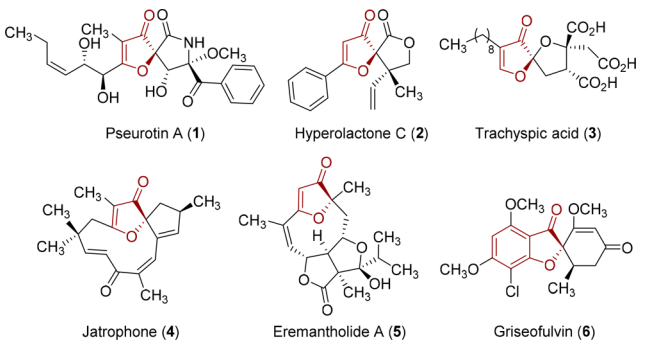


Figure 1. Representative natural products featuring the 3(2*H*)-furanone or benzo-3(2*H*)-furanone substructure.

Synthetic methods that enable flexible and stereoselective construction of highly substituted 3(2*H*)-furanones are valuable in accessing these families of natural products or analogs thereof. Conceptually, the stereochemistry at the C2 position can be established during the 3(2*H*)-furanone assembly or in subsequent transformations. Enantioselective alkylations and conjugate additions of achiral 3(2*H*)-furanones embody the latter approach, and powerful methodologies for controlling the C2 stereochemistry were reported. Most of the previous studies employed benzo-3(2*H*)-furanones however,[7] with only few reports focusing on 3(2*H*)-furanones.[8] In the context of enantioselective synthesis of two natural pseurotins, cephalimysins B and C, we have reported a single example of stereoselective 1,4-addition of a 3(2*H*)-furanone onto an alkynone catalyzed by nickel(II)−diamine complex **7** (Figure 2).[9] Since we found no precedent for the use of this catalyst in conjugate additions to alkynones,[10] we now disclose details of a study that examined 1,4-additions between differently substituted 2-alkoxycarbonyl-3(2*H*)-furanones and terminal alkynones under the catalysis of **7**. We included also two other types of π-electrophiles—an α-bromo enone and an α-benzyl

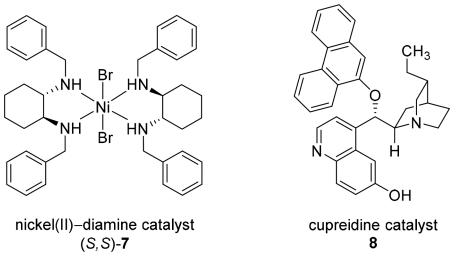


Figure 2. Structures of nickel(II)−diamine (*S*,*S*)-**7** and cupreidine derivative **8** employed as catalysts in this study.

Received: September 23, 2018

DOI: 10.1021/acs.orglett.8b03039
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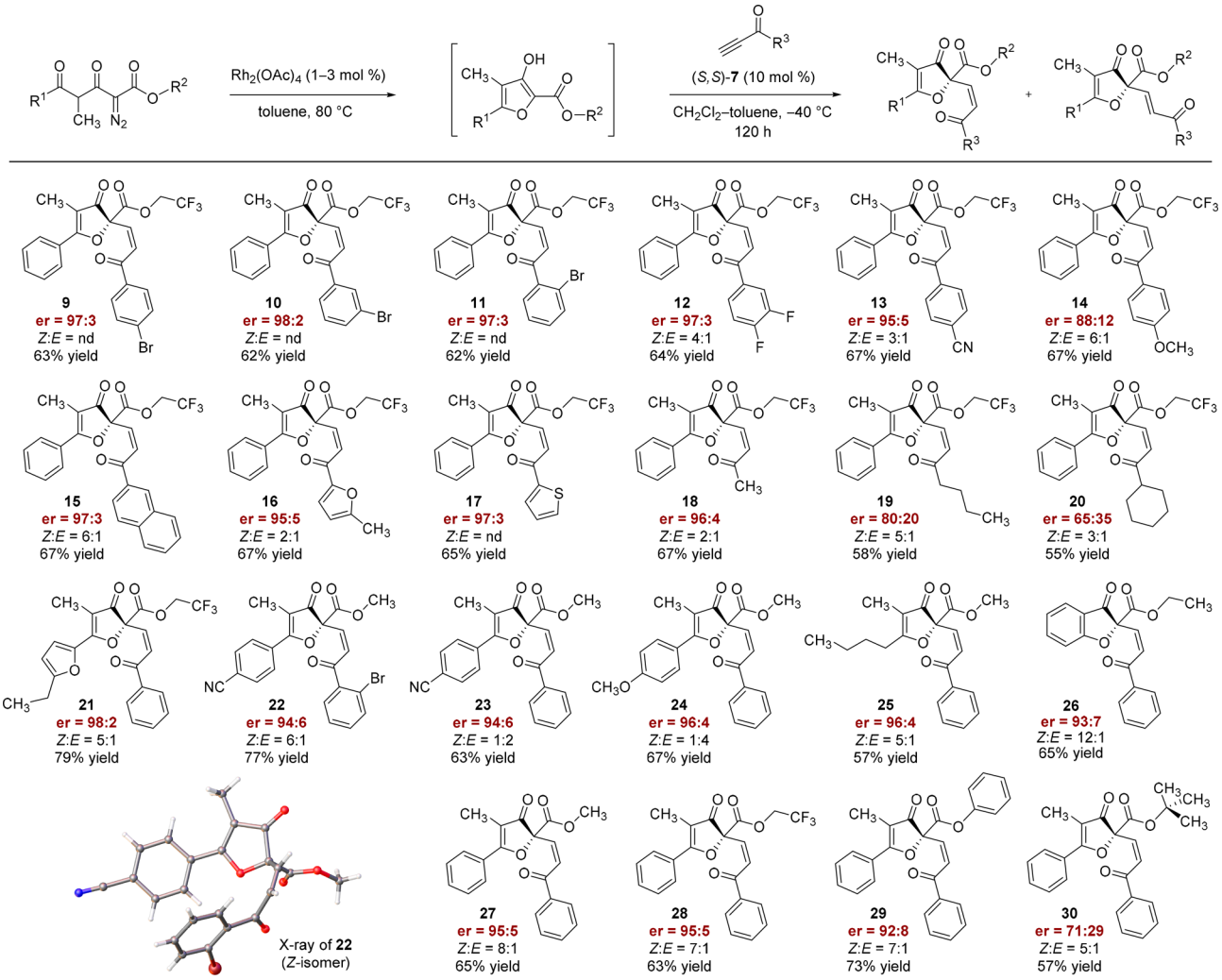
Scheme 1. Enantioselective 1,4-Additions of 2-Alkoxycarbonyl-3(2*H*)-furanones to Terminal Alkynones[a]



[a]The two-step single-flask transformation was carried out with 1.0 equiv of diazo carbonyl compound and 1.0 equiv of alkynone. The enantiomeric ratio (er) was determined by HPLC analysis of purified 1,4-adducts, while the *Z*/*E* ratio was determined by ^{1}H NMR analysis of the crude product mixture in acetone-d_6. The yield corresponds to the isolated yield of 1,4-adducts over two steps. The experiment leading to adduct **21** was carried out on a 0.9 mmol scale. Adduct **26** was prepared differently, starting from commercially available 2-ethoxylcarbonyl benzo-3(2*H*)-furanone (see SI). nd = not determined.

nitroalkene—as the corresponding 1,4-adducts can be readily elaborated to analogs of spirocyclic natural products pseurotins (see below).

To prepare a set of differently substituted 2-alkoxycarbonyl-3(2*H*)-furanones (R^1 and R^2 group), we relied on a highly efficient rhodium(II)-catalyzed cyclization of stable α-diazo carbonyl precursors (see Scheme 1).[11] Many of the prepared 2-alkoxycarbonyl-3(2*H*)-furanones had limited stability in solution and air oxidation (hydroxylation) at the nucleophilic C2 position was identified as one significant side reaction (see Supporting Information (SI)).[12]

With access to diverse 2-alkoxycarbonyl-3(2*H*)-furanones secured, we turned our attention to their enantioselective 1,4-additions to terminal alkynones. Due to the above-mentioned stability issues, we have adopted a general procedure, wherein 3(2*H*)-furanone formation and subsequent reaction with a π-electrophile were performed in a single flask[13] under an inert atmosphere. During the initial screening of catalysts, we found that nickel(II)−diamine complex **7** described by Evans and Seidel[14] provided the most promising levels of enantioselectivity (see SI) for the catalyst screening). Furthermore, the nickel(II)−diamine catalysis was essentially free of O-alkylation products, a known competing reaction pathway particularly pronounced for Michael additions to alkynones.[15] Indeed, O-alkylation was dominant with most of the cinchona alkaloid-derived catalysts we examined (see SI). The enantioselectivity of the nickel(II)−diamine-catalyzed process depends inversely on temperature (for *ent*-**21**: 88:12 er at 23 °C, 94:6 er at −20 °C, 97:3 er at −40 °C) and, critically, on conversion due to a rapid background (non-enantioselective) 1,4-addition during the workup.[16]

The mild reaction conditions permitted adoption of a 1:1 stoichiometry between the reacting partners, despite the above-mentioned stability issues of 2-alkoxycarbonyl-3(2*H*)-furanones. Our control experiments showed that the rate and the enantioselectivity of the 1,4-addition were not significantly affected by rhodium(II) residues carried over from the 3(2*H*)-furanone formation step.

DOI: 10.1021/acs.orglett.8b03039
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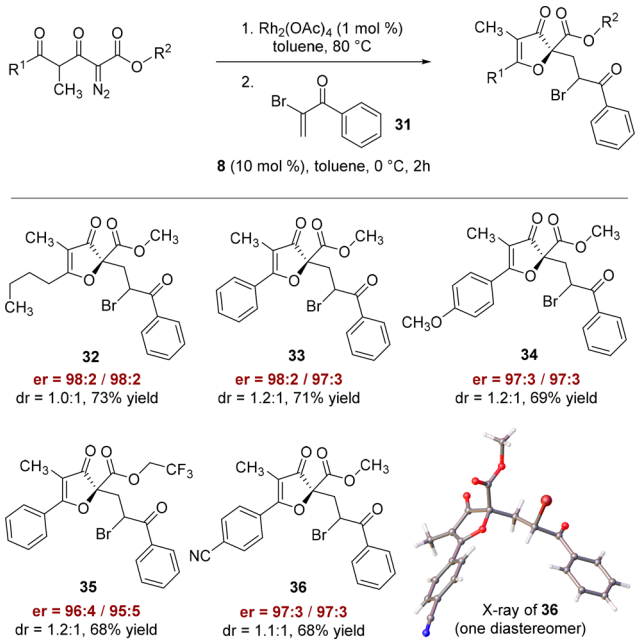
We examined over 20 different 3(2*H*)-furanone−alkynone combinations under our optimized conditions (10 mol % of (*S*,*S*)-**7**, −40 °C, 120 h), with the results depicted in Scheme 1. We were pleased to find that, in most cases, the 1,4-adducts were isolated in good enantiomeric ratio (er) and synthetically useful yields over the two steps. In terms of the electrophile structure, differently substituted aryl and heteroaryl alkynyl ketones (R^3) were accommodated. Lower enantioselectivities were observed mostly for alkyl alkynyl ketones (e.g., adducts **19** and **20**), with the interesting exception of methyl alkynyl ketone (adduct **18**). Variation in substitution at the 3(2*H*)-furanone component (R^1) had little influence on the reaction and good enantioselectivity was maintained across the different substrates examined (**21**−**25**, 94:6−98:2 er). The choice of ester group (R^2) located in the vicinity of the newly formed quaternary stereocenter is important. More specifically, methyl and trifluoroethyl esters gave comparably good results, while the enantioselectivity dropped for the larger phenyl and *tert*-butyl esters (compare adducts **27**, **28**, **29**, and **30**). Finally, adduct **26** (93:7 er) demonstrates that chiral benzo-3(2*H*)-furanones are also accessible by this methodology. While preferential formation of the *Z*-isomers was observed in most cases,[17] we note that the *Z* configuration is labile and, in consequence, the reported *Z*/*E* ratios may not accurately reflect the inherent selectivity (for example, *Z* → *E* isomerization was observed in deuterated chloroform by NMR).

The absolute configuration at the quaternary stereocenter established with nickel(II)−diamine (*S*,*S*)-**7** had previously been assigned by us as *R* through the conversion of adduct **21** to cephalimysin C (**44**).[9] To secure these previous assignments further, we have now determined the crystal structure of bromine-containing adduct **22** (Scheme 1, left bottom).[18] While a detailed mechanistic study would be required to rationalize the observed sense of asymmetric induction, our preliminary data support the formation of a nickel(II)-bound 3(2*H*)-furanone enolate (see SI).[14]

Changing the structure of the π-electrophile from a terminal alkynone to α-bromo enone **31** or α-benzyl nitroalkene **37** resulted in a dramatic decrease in enantioselectivity (see SI), pointing to limitations of the nickel(II)−diamine-based methodology. In order to re-establish good levels of enantioselectivity for these alternative Michael acceptors featuring a less frequently studied substitution pattern, we performed a new round of catalyst screening (see SI) and identified cupreidine derivative **8** (Figure 2) as a promising catalyst.[19] The catalyst was prepared by a single-step demethylation of a commercially available precursor (see SI). The presence of the 6′-hydroxyquinoline group in cupreidine **8** was found to be beneficial to the enantioselectivity and the rate of the 1,4-addition, in agreement with the original findings of Deng and colleagues.[20] As shown in Schemes 2 and 3, both α-bromo enone **31** and α-benzyl nitroalkene **37** readily participated in enantioselective conjugate additions in the presence of catalytic amounts of **8** (10 mol %, 0−23 °C, 1−2 h) and provided the corresponding 1,4-adducts in the er range 90:10−98:2.

The enantioselectivity was only moderately dependent on the reaction temperature. The diastereoselectivity (1,3-stereochemical relationship) proved difficult to control under these and many other conditions attempted (see SI). Control experiments performed with nitroalkene adduct **41** suggest that the low diastereoselectivity is not a consequence of a rapid epimerization under the reaction conditions.

Scheme 2. Enantioselective 1,4-Additions of 2-Alkoxycarbonyl-3(2*H*)-furanones to α-Bromo Enone[a]



[a]The two-step single-flask transformation was carried out with 1.0 equiv of diazo carbonyl and 1.0 equiv of α-bromo enone. The enantiomeric ratio (er) was determined by HPLC analysis of the purified 1,4-adducts, while the diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude product mixture. The yield corresponds to the combined isolated yield for both diastereomers over two steps.

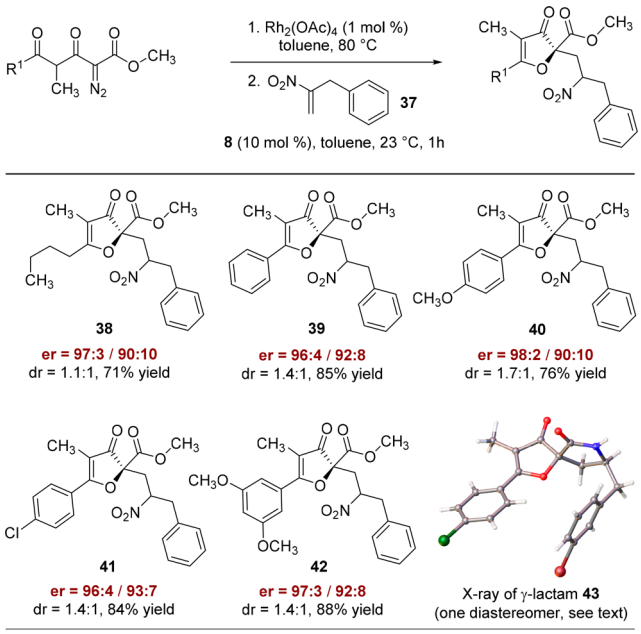
The absolute configuration of the 1,4-adducts obtained under cupreidine **8** catalysis was determined by X-ray crystallography. The crystal structure of α-bromo enone adduct **36** (Scheme 2) revealed the *S* configuration at position C2, which is opposite to that observed above for alkynones with nickel(II)−diamine (*S*,*S*)-**7**.[21] Reductive debromination (zinc, acetic acid) performed on a diastereomeric mixture of enantiomerically enriched α-bromo adduct **35** further confirmed that both diastereomers have the same absolute configuration at the quaternary stereocenter (see SI). For α-benzyl nitroalkene adducts, the absolute configuration at the quaternary stereocenter was the same (*S*), as determined after a single-step conversion of a nitroalkene adduct into spirocyclic lactam **43** (X-ray in Scheme 3).

The three types of 1,4-adducts described in Schemes 1−3 can be elaborated further (Scheme 4). We have shown previously that alkynone adduct **21** is a synthetic precursor of natural product cephalimysin C (**44**).[9] To convert α-bromo enone adduct **35** into an analogous spirocyclic furanone−γ-lactam (**45**), the bromide was first displaced with sodium azide, and subsequent treatment with tri-*n*-butylphosphine promoted a reductive cyclization. α-Benzyl nitroalkene adduct **39** underwent lactamization to **46** directly upon exposure to zinc in acetic acid (see SI for additional examples).

In summary, we have shown that nickel(II)−diamine complex **7** is a useful catalyst for enantioselective 1,4-additions of in situ generated 2-alkoxycarbonyl-3(2*H*)-furanones onto various terminal alkynones. The method yields enantiomeri-

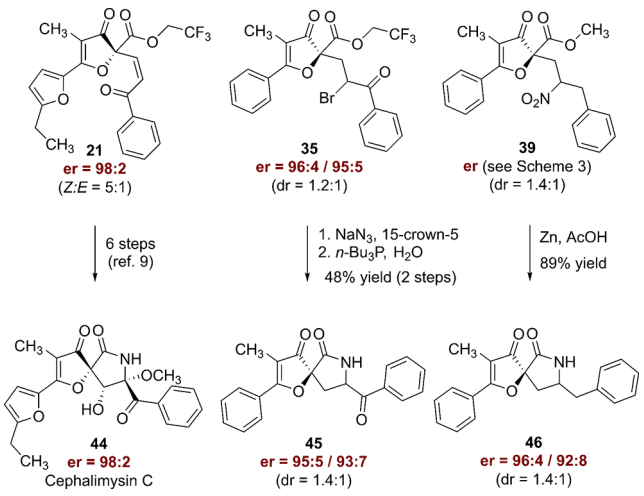
DOI: 10.1021/acs.orglett.8b03039
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Enantioselective 1,4-Additions of 2-Alkoxycarbonyl-3(2*H*)-furanones to α-Benzyl Nitroalkene[a]



[a]The two-step single-flask reaction was carried out with 1.0 equiv of diazo carbonyl and 1.0 equiv of α-benzyl nitroalkene. The enantiomeric ratio (er) was determined by HPLC analysis after conversion of the 1,4-adducts into spirocyclic lactams (see SI). The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product mixture. The yield corresponds to the combined isolated yield for both diastereomers over two steps.

Scheme 4. Elaboration of Prepared 1,4-Adducts into Spirocyclic Furanone−γ-Lactams



cally enriched 1,4-adducts that are free of undesired O-alkylation products. While the nickel(II)−diamine-catalyzed process did not extend to other types of π-electrophiles examined—α-bromo enone **31** and α-benzyl nitroalkene **37**—catalysis by cupreidine derivative **8** provided a useful alternative. All prepared 1,4-adducts are highly functionalized chiral molecules featuring a quaternary stereocenter at the 3(2*H*)-furanone ring that may find applications in natural product synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03039.

Detailed experimental procedures and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1866443−1866447 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: svenda@chemi.muni.cz.

ORCID

Jakub Švenda: 0000-0001-9232-3218

Author Contributions

[§]P.V. and D.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support provided by the Marie Curie Career Integration Grant (322001), the Bader Philanthropies grant (17573), and the National Program of Sustainability II (LQ1605) funded by MEYS CR. We acknowledge the CIISB research infrastructure project (X-ray Core Facility, LM2015043) and the National Infrastructure for Chemical Biology (CZ-OPENSCREEN, LM2015063) funded by MEYS CR. We thank Prof. Tibor Soós (Hungarian Academy of Sciences) for providing us with the squaramide-based catalysts.

■ REFERENCES

(1) Bloch, P.; Tamm, C.; Bollinger, P.; Petcher, T. J.; Weber, H. P. *Helv. Chim. Acta* **1976**, *59*, 133−137.

(2) Aramaki, Y.; Chiba, K.; Tada, M. *Phytochemistry* **1995**, *38*, 1419−1421.

(3) Shiozawa, H.; Takahashi, M.; Takatsu, T.; Kinoshita, T.; Tanzawa, K.; Hosoya, T.; Furuya, K.; Takahashi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 357−362.

(4) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Renauld, J. A. S.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 4476−4477.

(5) Raffauf, R. F.; Huang, P.-K. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975**, *97*, 6884−6886.

(6) Oxford, A. E.; Raistrick, H.; Simonart, P. *Biochem. J.* **1939**, *33*, 240−248.

(7) (a) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307−7313. (b) Ogawa, C.; Kizu, K.; Shimizu, H.; Takeuchi, M.; Kobayashi, S. *Chem. - Asian J.* **2006**, *1*, 121−124. (c) Dong, N.; Li, X.; Wang, F.; Cheng, J.-P. *Org. Lett.* **2013**, *15*, 4896−4899. (d) Zhang, Z.-P.; Dong, N.; Li, X.; Cheng, J.-P. *Org. Biomol. Chem.* **2015**, *13*, 9943−9947. (e) Wang, H.; Wang, Y.; Zhang, C.; Jiang, Y.; Chu, M.; Li, Z.; Du, X.; Xu, D. *Org. Biomol. Chem.* **2017**, *15*, 4191−4198. (f) Zhao, L.; Huang, G.; Guo, B.; Xu, L.; Chen, J.; Cao, W.; Zhao, G.; Wu, X. *Org. Lett.* **2014**, *16*, 5584−

DOI: 10.1021/acs.orglett.8b03039
Org. Lett. XXXX, XXX, XXX−XXX

5587. (g) Sivamuthuraman, K.; Kumarswamyreddy, N.; Kesavan, V. *J. Org. Chem.* **2017**, *82*, 10812−10822. (h) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928−3930. (i) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem. - Eur. J.* **2008**, *14*, 128−135. (j) Yu, J.-S.; Liao, F.-M.; Gao, W.-M.; Liao, K.; Zuo, R.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 7381−7385. (k) Fu, J.; Shang, H.; Wang, Z.; Chang, L.; Shao, W.; Yang, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4198−4202. (l) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226−4228. (m) Yan, L.; Huang, G.; Wang, H.; Xiong, F.; Peng, H.; Chen, F. *Eur. J. Org. Chem.* **2018**, 99−103.

(8) (a) He, W.; Jing, L.; Qin, D.; Wang, R.; Xie, X.; Wu, S. *Tetrahedron Lett.* **2013**, *54*, 6363−6365. (b) He, W.; Jing, L.; Qin, D.; Xie, X.; Wu, S.; Wang, R. *Tetrahedron Lett.* **2014**, *55*, 209−211. (c) Du, C.; Li, L.; Li, Y.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7853−7856. (d) Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 10658−10662.

(9) Chalupa, D.; Vojáčková, P.; Partl, J.; Pavlović, D.; Nečas, M.; Švenda, J. *Org. Lett.* **2017**, *19*, 750−753.

(10) For recent reports on enantioselective conjugate additions of 1,3-dicarbonyls to alkynones, see: (a) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672−5673. (b) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2218−2220. (c) Lan, Q.; Wang, X.; Shirakawa, S.; Maruoka, K. *Org. Process Res. Dev.* **2010**, *14*, 684−686. (d) Zhang, Z.; Liu, X.; Wang, Z.; Zhao, X.; Lin, L.; Feng, X. *Tetrahedron Lett.* **2014**, *55*, 3797−3801.

(11) (a) Bien, S.; Gillon, A. *Tetrahedron Lett.* **1974**, *15*, 3073−3074. (b) Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 489−492. (c) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820−829. (d) See ref 8c.

(12) (a) Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3607−3608. (b) Davey, A. E.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 25−27. (c) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657−2666. (d) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77−83. (e) Truong, P.; Xu, X.; Doyle, M. P. *Tetrahedron Lett.* **2011**, *52*, 2093−2096.

(13) For the recent reviews on single-flask (one-pot) operations in synthesis, see: (a) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607. (b) Hong, B. C.; Raja, A.; Sheth, V. M. *Synthesis* **2015**, *47*, 3257−3285. (c) Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866−880.

(14) (a) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958−9959. (b) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583−11592.

(15) (a) Tae, J.; Kim, K.-O. *Tetrahedron Lett.* **2003**, *44*, 2125−2128. (b) See ref 10a.

(16) We have reported previously that silica gel readily promotes the 1,4-addition (see ref 9).

(17) The observed *Z*-selectivity is suggested to be an outcome of a kinetic protonation of an allenolate intermediate from the more accessible π-face. The exact role of nickel(II)−diamine **7** in this process is unclear, as *Z*-selective additions were also observed with *N,N*-diisopropylethylamine as the catalyst (see SI).

(18) The opposite absolute configuration at C2 (*S*) can be obtained using an enantiomeric nickel(II)−diamine catalyst [(*R,R*)-**7**; see ref 9].

(19) See ref 7h. It is worth noting that cupreidine catalyst **8** performed poorly with terminal alkynones as π-electrophiles (see SI).

(20) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906−9907.

(21) The opposite absolute configuration at C2 (*R*) can be obtained using a cupreine-based catalyst (structure **66** in SI), though with lower levels of enantioselectivity [e.g., adduct **35** (0 °C): er = 13:87/14:86; adduct **39** (0 °C): er = 9:91/17:83].

DOI: 10.1021/acs.orglett.8b03039
Org. Lett. XXXX, XXX, XXX−XXX