Organic LETTERS

Letter

pubs.acs.org/OrgLett

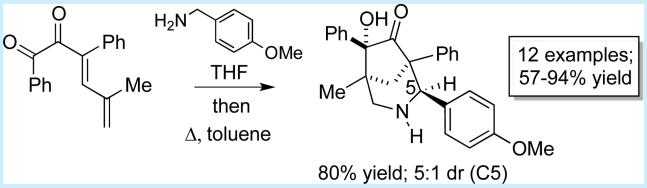
Nazarov Cyclization/Internal Redox Cyclization Sequence for the Synthesis of N-Heterocyclic Bridged Ring Systems

Yu-Wen Huang and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216, United States

Supporting Information

ABSTRACT: A 1,6 conjugate addition/Nazarov electrocyclization/internal redox cyclization sequence was developed. Various 5-hydroxycyclopentenones were made through the 1,6-conjugate addition initiated Nazarov reaction with excellent diastereoselectivities. Under thermal conditions, these underwent a through-space 1,5-hydride-transfer/ring-closure reaction to form bridged bicyclic N-heterocyclic compounds with up to four stereogenic centers. It was also possible to convert simple acyclic dienyl diketones into the bicyclo[3.2.1] products in a one-pot process (with a solvent switch).

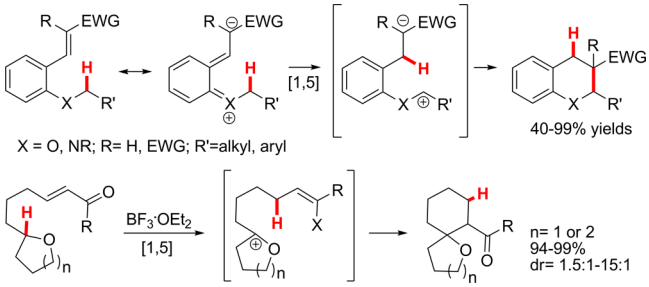


Modern drug discovery efforts depend upon high-throughput screening of small molecule libraries rich in structural diversity and filled with compounds that occupy biologically relevant chemical space and possess "lead-like" characteristics.[1] Several studies have provided insight into the physicochemical properties that characterize bioactive leads, especially the molecules that survive clinical trials and become drugs.[1a,2] However, existing libraries contain few compounds with these desirable properties;[3] instead, sample collections are composed of molecules that are simple, achiral, and structurally similar to one another.[4] It is also acknowledged that medicinal chemists in industry use a limited arsenal of "easy" methods that can be automated, meaning that three-dimensional, stereochemically complex molecules are rarely synthesized as part of drug discovery efforts.[1e,5] New cyclization methods that are safe, inexpensive, and operationally simple and allow rapid synthesis of complex polar molecules from simple precursors are needed to enrich compound collections for drug discovery programs.

Recently, methods for C(sp^3)−H bond functionalization through internal redox/cyclization processes have been studied extensively.[6] These cascades begin with intramolecular transfer of an activated hydride (e.g., **H**−C−X where X is electron-releasing) to a Michael acceptor, generating a carbocation stabilized by the X substituent (see intermediates in brackets, Scheme 1). Subsequently, intramolecular capture of the new carbocation leads to formation of a new ring. In numerous examples of the internal redox cascade cyclization, substrates have an aromatic ring as a scaffold, linking the donor C−H bond and the acceptor (Scheme 1, top). The reactions are induced thermally or catalyzed by Lewis acids, phosphoric acids, or L-proline derivatives, and the hydride transfer step is considered by many to be a pericyclic 1,5 hydride shift in these cases.[6e,f]

More rarely, the hydride transfer occurs through space, and depending on the scaffold, the subsequent cyclization can deliver linear fused,[7] spiro-fused (e.g., Scheme 1 bottom),[8] or bridged[7e,9] ring systems.[10]

Scheme 1. Examples of Internal Redox/Ring-Closure Reactions[6,8a]



We have recently discovered an internal redox cyclization of this more uncommon variety, involving a through-space hydride transfer/Mannich cyclization, to generate bicyclo[3.2.1] ring systems with high efficiency (conversion of **2** to **3**, Scheme 2). In the overall sequence, dienyl diketones **1** were converted into bicycles **3**, generating four new bonds, two rings, and four stereogenic centers (at C2, C3, C5, and C6) with good yields and diastereoselectivities.

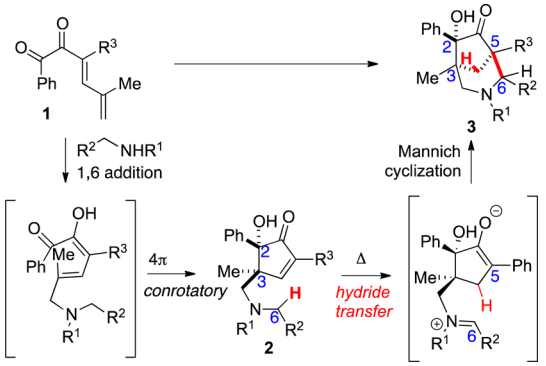
To examine the internal redox cascade cyclization of interest, we first prepared a series of α-hydroxy cyclopentanones **2** as single isomers using our 1,6-conjugate addition/Nazarov cyclization sequence (Scheme 3).[11]

Electron-rich arylamines, electron-deficient arylamines, and alkylamines were all competent nucleophiles. Generally, secondary amines were nucleophilic enough that they did not require Lewis acid or base to reach full conversion, and the reactions were complete within 4 h. When less nucleophilic

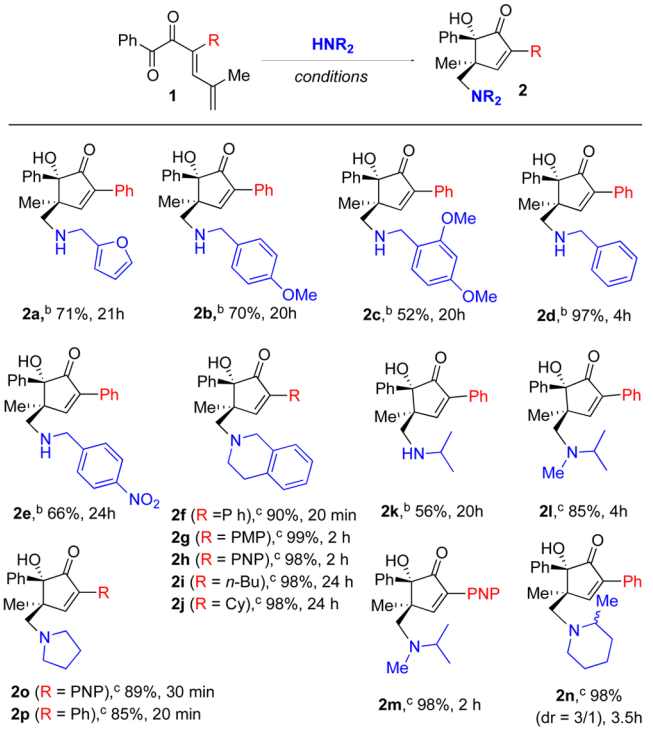
Received: August 8, 2016

DOI: 10.1021/acs.orglett.6b02369
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of Bridged Ring Systems through an Internal Redox Cyclization Sequence



Scheme 3. 5-Hydroxycyclopentenones Generated via 1,6-Conjugate Addition-Initiated Nazarov Cyclization[a]

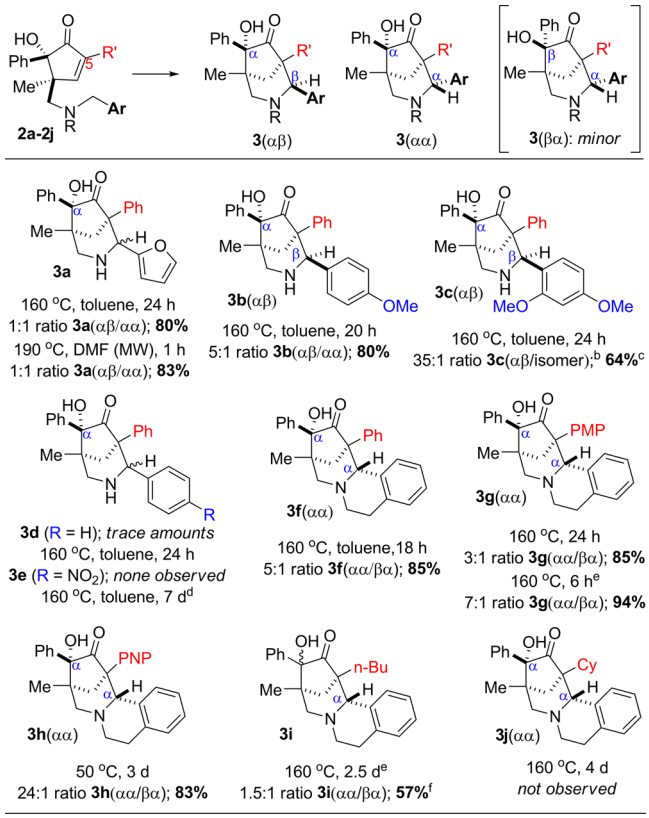


[a]PMP = *p*-methoxyphenyl; PNP = *p*-nitrophenyl; Cy = cyclohexyl. [b]Reaction conditions: $Y(OTf)_3$ (1 mol %), LiCl (2.0 equiv), Et_3N (1.0 equiv), nucleophile (1.05 equiv), THF (0.1 M) [c]Reaction conditions: nucleophile (1.05 equiv), THF (0.1 M).

primary amines were employed, Lewis acid and an amine base were required to catalyze the reaction.

In initial studies, we studied the reactivity of furylamine adduct **2a**. Under simple thermal conditions (toluene, 160 °C), the redox cyclization is complete after 24 h, and a 1:1 mixture of diastereoisomers (**3a**($\alpha\alpha/\alpha\beta$); epimeric at C6) is obtained in 80% combined yield (Scheme 4).[12] The structural assignment was made by analysis of X-ray data for **3a**($\alpha\alpha$) and corroborated with NMR data (see Supporting Information). Lewis acid additives did not improve the reaction rate; adding catalytic amounts of $Sc(OTf)_3$, $Yb(OTf)_3$, and BF_3/Et_2O produced a complex mixture of products. The reaction time was reduced to 1 h using DMF as solvent and heating to 190 °C in a microwave (Scheme 4).

Scheme 4. Internal Redox Cyclizations of Arylamines[a]



[a]Reaction conditions: sealed tube, toluene at the specified temperature. PMP = *p*-methoxyphenyl; PNP = *p*-nitrophenyl; Cy = cyclohexyl. [b]The structure of the minor isomer was not determined. [c]29% of 2,4-dimethoxybenzaldehyde was obtained. [d]50−60% conversion. [e]3 equiv of $PhCO_2H$ was used as additive. [f]30% of **2i** was recovered.

The results of cyclizations conducted on a series of adducts **2** are shown in Scheme 4. Amines bearing electron-rich aryl groups such as furyl (**2a**), 4-methoxybenzyl (**2b**), or 2,4-dimethoxybenzyl (**2c**) generated the desired products in good yields. Diastereoselectivity improved with increased steric bulk on the aromatic ring. In substrates without an electron-donating aromatic ring, such as benzyl (**2d**) and *p*-nitrobenzyl (**2e**), the corresponding products **3d** and **3e** were not formed efficiently (Scheme 4). However, hydride transfer in the cyclic tetrahydroisoquinoline substrate **2f** was both efficient and diastereoselective, affording **3f** in 85% yield after 18 h.[13] Notably, in the reaction of cyclic amine **2f**, the aryl group at C6 is installed with a stereogenicity, whereas redox cyclizations of the acyclic amines **2b** and **2c** selectively install the aryl group at C6 with β orientation. In the reactions of **2c** and **2f**, only one C6 epimer was observed, along with a small amount of an isomeric compound. The minor isomer in the reaction of **2f** was tentatively identified as the C2 epimer **3f**($\beta\alpha$); see Scheme 4.[14]

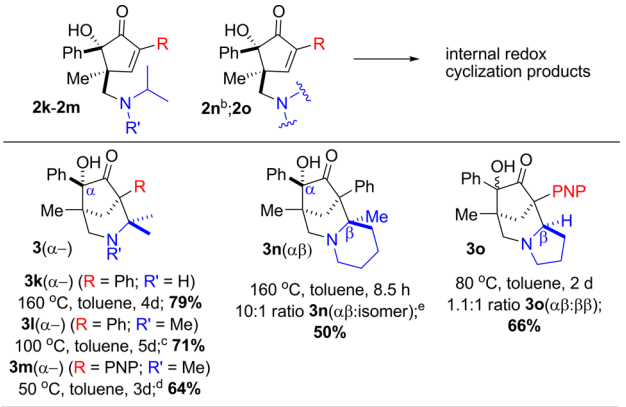
Different C5 substituents (R′; Scheme 4) are tolerated and correlate to changes in reaction efficiency. Substrates **2f** and **2g**, with electron-neutral and electron-rich R′ groups, respectively, underwent smooth redox cyclization to produce **3f**($\alpha\alpha$) and **3g**($\alpha\alpha$) as the major products. In the presence of 3 equiv of benzoic acid, it was possible to shorten the reaction time of **2g** from 24 to 6 h and increase the diastereoselectivity from 3:1 to

DOI: 10.1021/acs.orglett.6b02369
Org. Lett. XXXX, XXX, XXX−XXX

7:1.[15] When R′ is a *p*-nitrophenyl group (**2h**), the reaction occurred at significantly lower temperature (50 °C) with excellent yield and diastereoselectivity. Alkyl groups such as *n*-butyl (**2i**) and cyclohexyl (**2j**) were also tested. Compound **3i**($\alpha\alpha$) was obtained in good yield (57%, 87% brsm), but no hydride transfer occurred in the reaction of **2j**. In this case, the steric bulk of the cyclohexyl group could prevent the molecule from achieving the stereoelectronic overlap necessary for hydride transfer.

To test whether the hydride-transfer step requires an arylamine donor (as in substrates **2a-2j**, Scheme 4), we subjected substrates bearing aliphatic amine donors to the reaction conditions (Scheme 5).

Scheme 5. Internal Redox Cyclizations of Alkylamines[a]



[a]Reaction conditions: sealed tube, toluene, at the specified temperature. PNP = *p*-nitrophenyl. [b]Reactant **2n** was a 3:1 mixture of diastereoisomers. [c]3 equiv of $PhCO_2H$ was used as additive. [d]79% conversion. [e]The structure of the minor isomer was not determined.

The study began with isopropylamine substrates **2k–m** (see Scheme 3). Under thermal conditions, the desired product **3k**(α-) was obtained in 79% yield from secondary isopropylamine **2k**. In the reaction of tertiary *N*-methylisopropylamine **2l**, the highest yield was obtained with 3 equiv of benzoic acid, affording **3l**(α-) in 71% yield after 5 days.[15] Consistent with previous results (see Scheme 4), the reaction was more facile in substrates containing the *p*-nitrophenyl group. Selective hydride transfer/cyclization of **2m** was observed at 50 °C in toluene, without additive, to produce **3m**(α-) in 64% yield after 3 days (79% conversion).

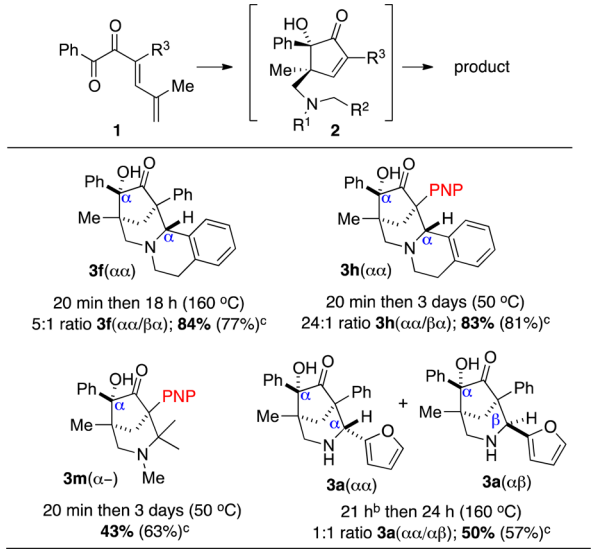
It was also possible to cyclize aliphatic nitrogen heterocycles (Scheme 5). Piperidine derivative **2n** reacted to give tricycle **3n**($\alpha\beta$) with good yield and diastereoselectivity. Pyrrolidine derivative **2o** underwent the reaction to deliver **3o**($\alpha\beta/\beta\beta$; ~1:1 ratio), with complete control of stereochemistry at C6, the hydride shift center. The success of this transformation is notable because hydride transfer from pyrrolidine did not occur in substrate **2p** (Scheme 3), suggesting that substrates **2** with electron-withdrawing substituents on the enone are not only better hydride acceptors but may enjoy broader substrate scope in these redox cyclizations.

The trends observed indicate that reactions are most efficient for substrates with (1) secondary amine donors, (2) an electron-donating aromatic R^2 substituent, and (3) an electron-deficient (enone) hydride acceptor. The amine lone pair and electron-donating R^2 substituents should both facilitate the development of positive charge on C6 (Scheme 2) in the transition state leading to hydride transfer. When a substrate contains an electron-deficient enone, the hydride transfer is even more facile, and donors without strong cation-stabilizing R^2 substituents participate (see Scheme 5).

At this point, the factors governing stereocontrol in these reactions are not well understood. We do not know whether the diastereoselectivity-determining step for the C6 stereocenter is the Mannich cyclization or the hydride transfer,[16] and we do not know how the C2 stereocenter epimerizes (Scheme 2 shows the proposed reaction sequence with carbon numbers). At this point, our experimental results indicate that neither the reactants **2** nor the products **3** undergo isomerization at C2 under the reaction conditions used for hydride transfer/Mannich ring closure (see the Supporting Information). Ongoing studies in the laboratory are focused on gaining a better understanding of the stereochemical outcomes of these reactions.

Finally, we have shown that it is possible to convert dienyl diketones **1** into the bicyclo[3.2.1] products in a one-pot process to build complex heterocyclic molecules with up to four stereocenters (Scheme 6). Bridged systems **3f**($\beta\alpha$) and **3h**($\beta\alpha$) were obtained in excellent yields and good to excellent diastereoselectivities. We were also able to obtain **3m**(α-) and **3a**($\alpha\alpha/\alpha\beta$) using the one-pot protocol.

Scheme 6. One-Pot 1,6-Conjugate Addition/Nazarov Cyclization/Internal Redox Cyclization[a]



[a]Reaction conditions: amine nucleophile (1.05 equiv) THF, rt; remove THF (rotovap), add toluene, and heat in sealed tube at the specified temperature, unless otherwise noted. PNP = *p*-nitrophenyl. [b]Amine nucleophile (1.05 equiv), 1 mol % of $Y(OTf)_3$, 2 equiv of LiCl, and Et_3N, THF, rt. [c]The yield in parentheses was obtained using the stepwise (two-pot) procedure.

In summary, we have developed a new reaction sequence that enables the rapid assembly of nitrogen-containing [3.2.1] ring systems from acyclic, achiral dienyl diketones. The sequence, which can be conducted in one pot (with a solvent switch), involves 1,6 addition of an amine, Nazarov cyclization, and finally, internal redox cyclization. Overall, it is possible to install up to four stereogenic centers, including a tertiary alcohol and two all-carbon quaternary centers using this methodology. Additional studies in our laboratory are focused

DOI: 10.1021/acs.orglett.6b02369
Org. Lett. XXXX, XXX, XXX–XXX

on expanding the scope of the sequence and on understanding the stereochemical outcomes observed in the internal redox cyclization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. Synthetic procedures; ^{1}H, ^{13}C NMR spectra for all new compounds; X-ray data for **3a**($\alpha\alpha$) and **3f**($\alpha\alpha$) (PDF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02369.

X-ray data for **3a**($\alpha\alpha$) (CIF)
X-ray data for **3f**($\alpha\alpha$) (CIF)
Synthetic procedures; ^{1}H, ^{13}C NMR spectra for all new compounds; X-ray data for **3a**($\alpha\alpha$) and **3f**($\alpha\alpha$) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: frontier@chem.rochester.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1565813) for funding this work. We are grateful to Dr. Furong Sun (University of Illinois, Urbana−Champaign) for HRMS analysis and to Dr. William W. Brennessel (University of Rochester) for performing X-ray crystallography.

■ REFERENCES

(1) (a) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405. (b) Doveston, R.; Marsden, S.; Nelson, A. *Drug Discovery Today* **2014**, *19*, 813. (c) Barker, A.; Kettle, J. G.; Nowak, T.; Pease, J. E. *Drug Discovery Today* **2013**, *18*, 298. (d) López-Vallejo, F.; Giulianotti, M. A.; Houghten, R. A.; Medina-Franco, J. L. *Drug Discovery Today* **2012**, *17*, 718. (e) Hann, M. M.; Keserü, G. M. *Nat. Rev. Drug Discovery* **2012**, *11*, 355. (f) Wild, H.; Heimbach, D.; Huwe, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7452.

(2) (a) Lachance, H.; Wetzel, S.; Kumar, K.; Waldmann, H. *J. Med. Chem.* **2012**, *55*, 5989. (b) Vasilevich, N. I.; Kombarov, R. V.; Genis, D. V.; Kirpichenok, M. A. *J. Med. Chem.* **2012**, *55*, 7003. (c) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(3) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114.

(4) (a) O' Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104. (c) Schreiber, S. L. *Nature* **2009**, *457*, 153.

(5) (a) Keserue, G. M.; Makara, G. M. *Nat. Rev. Drug Discovery* **2009**, *8*, 203. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(6) For reviews, see: (a) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, *2006*, 2625. (b) Pan, S. C. *Beilstein J. Org. Chem.* **2012**, *8*, 1374. (c) Wang, M. *ChemCatChem* **2013**, *5*, 1291. (d) Peng, B.; Maulide, N. *Chem. - Eur. J.* **2013**, *19*, 13274. (e) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010. (f) Wang, L.; Xiao, J. *Adv. Synth. Catal.* **2014**, *356* (6), 1137−1171.

(7) (a) Atkinson, R. S. *J. Chem. Soc. D* **1969**, 735a. (b) Atkinson, R. S.; Green, R. H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 394. (c) Mahoney, S. J.; Moon, D. T.; Hollinger, J.; Fillion, E. *Tetrahedron Lett.* **2009**, *50*, 4706. (d) Mori, K.; Sueoka, S.; Akiyama, T. *Chem. Lett.* **2011**, *40*, 1386. (e) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424. (f) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744.

(8) (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (b) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (c) Jiao, Z.-W.; Zhang, S.-Y.; He, C.; Tu, Y.-Q.; Wang, S.-H.; Zhang, F.-M.; Zhang, Y.-Q.; Li, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8811.

(9) (a) Ten Broeke, J.; Douglas, A. W.; Grabowski, E. J. J. *J. Org. Chem.* **1976**, *41*, 3159. (b) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, *2004*, 90. (c) Frank, É.; Schneider, G.; Kádár, Z.; Wölfling, J. *Eur. J. Org. Chem.* **2009**, *2009*, 3544.

(10) Internal redox cyclizations have also been initiated by a through-space hydride shift to an alkyne activated by a transition metal; see: (a) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543−3552. (b) Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133* (20), 7696−7699.

(11) (a) Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454. (b) Brooks, J. L.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 16551. Brooks, J. L.; Frontier, A. J. *J. Am. Chem. Soc.* **2013**, *135*, 19362 (correction). (c) Brooks, J. L.; Huang, Y.-W.; Frontier, A. J. *Org. Synth.* **2014**, *91*, 93. (d) Jacob, S. D.; Brooks, J. L.; Frontier, A. J. *J. Org. Chem.* **2014**, *79*, 10296.

(12) Compound numbering: The stereochemistry at C2 and C6 is given in parentheses for each compound, as indicated in Schemes 4−6.

(13) The relative stereochemistry of **3f**($\alpha\alpha$) was unambiguously determined by X-ray crystallographic analysis.

(14) The minor isomers **3**($\beta\alpha$) in the 1,2,3,4-tetraisoquinoline cases were characterized via the nuclear Overhauser effect and COSY spectra (see the Supporting Information).

(15) In general, benzoic acid-catalyzed cyclizations occurred at lower temperatures and gave higher diastereoselectivities.

(16) The hydride transfer step has been demonstrated to be stereochemistry-determining in related systems; see: (a) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. See also: (b) Chen, L.; Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem. - Eur. J.* **2012**, *18*, 8891. With a "barrierless" C−C bond formation, see: (c) Zhang, L.; Chen, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem. - Asian J.* **2012**, *7*, 2569.

DOI: 10.1021/acs.orglett.6b02369
Org. Lett. XXXX, XXX, XXX−XXX