Total Synthesis of (−)-Nodulisporic Acid D

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Total Synthesis of (−)-Nodulisporic Acid D

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Supporting Information

ABSTRACT: A convergent total synthesis of the architecturally complex indole diterpenoid (−)-nodulisporic acid D has been achieved. Key synthetic transformations include vicinal difunctionalization of an advanced α,β-unsaturated aldehyde to form the E,F-trans-fused 5,6-ring system of the eastern hemisphere and a cascade cross-coupling/indolization protocol leading to the CDE multisubstituted indole core.

The nodulisporic acids (**1**−**4**) comprise a family of secondary metabolites (Figure 1), isolated from *Nodulisporium* sp. by

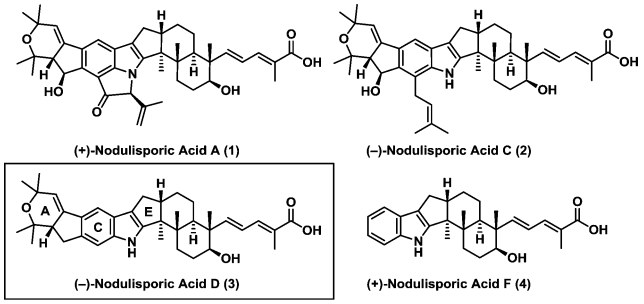


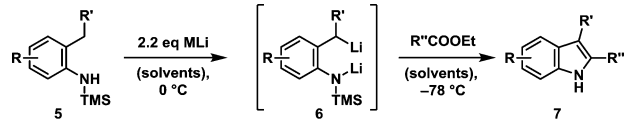
Figure 1. Nodulisporic acids.

Ondeyka and co-workers at the Merck Research Laboratories.[1] As a family, the nodulisporic acids display unique biological activity against insects but are devoid of side effects in mammals.[2] As such the nodulisporic acids hold promise as systemic insecticides.[3] In conjunction with our long-standing interest in the construction of architecturally complex indole diterpenoids, we launched a campaign toward the total synthesis of the nodulisporic acids, initially leading to the completion of (+)-nodulisporic acid F (**4**).[4] Herein, we report the first total synthesis of the more complex (−)-nodulisporic acid D (**3**).

As a class, the nodulisporic acids derive presumably via the metabolic machinery leading to paxilline, penitrem, and related diterpene alkaloids, recently reconstituted biosynthetically,[5] that require addition of isoprenyl units to generate the dihydropyran ring, and/or the tricyclic indole/indoline core, along with the dienoic acid side chain, all of which conspire to increase their complexity and in turn the synthetic challenge.[6]

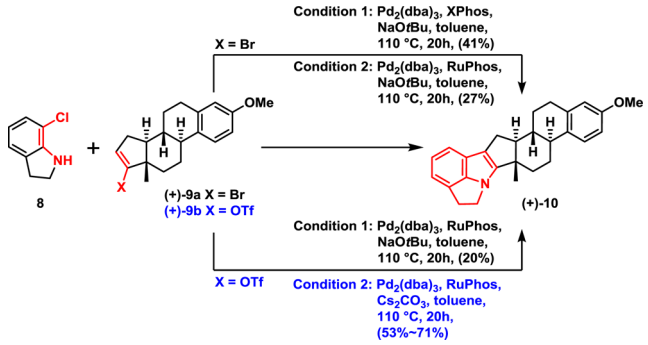
For the synthesis of nodulisporic acids A (**1**) and D (**3**), we initially envisioned exploiting the two-component indole construction tactic that early on we had devised involving the union of dianions (e.g., **6**) derived from ortho-alkyl N-TMS substituted anilines (**5**) with esters and lactones that permit access to the indole nuclei (**7**) (Scheme 1),[7] and in turn permitted access to a variety of diterpene indole alkaloids, including (−)-21-isopentenylpaxilline,[8] (−)-penitrem D,[9] and (+)-nodulisporic acid F (**4**).[6]

Scheme 1. A Two-Component Indole Construction Tactic



Application of this tactic to nodulisporic acids A and D however resulted in significant difficulties, presumably arising from the sensitivity of the targets.[6] Notwithstanding this setback, we continued to favor a convergent approach, wherein two fragments would be united via construction of the central indole ring. Toward this end, we turned to the palladium mediated cascade reaction introduced by Barluenga and co-workers[10] (Scheme 2). Application of this reaction sequence (X = Br) to

Scheme 2. Development of an Indole Construction Tactic



construction of a model [(+)-**10**] of the distorted tricyclic indole/indoline core, found in (+)-nodulisporic acid A (**1**),[11] employing chloroindoline **8** and vinyl bromide (+)-**9a**, proved encouraging, albeit the yield of (+)-**10** was moderate (27−41%). We reasoned that the more readily available vinyl triflates, now employed in a variety of Buchwald−Hartwig aminations,[12] might improve the Barluenga indolization protocol. Pleasingly, we discovered that the combination of $Pd_2(dba)_3$ and RuPhos[13] with **8** and vinyl triflate (+)-**9b**, in conjunction with the less basic cesium carbonate, furnished (+)-**10** in 53% to 71% yield.

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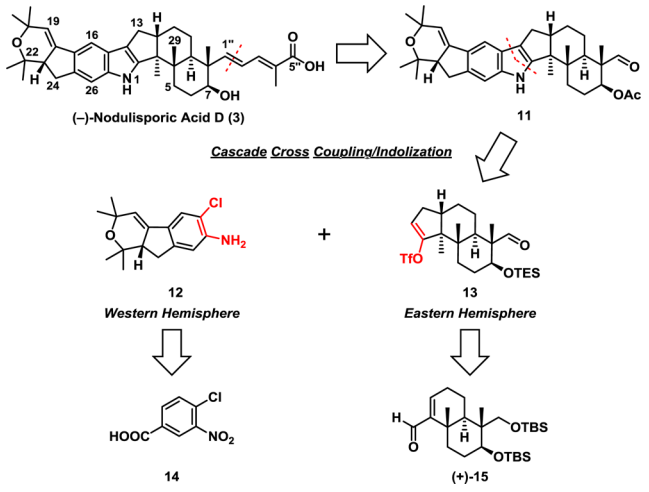
With this indole construction tactic available, we turned to (−)-nodulisporic acid D (**3**). From the retrosynthetic perspective, we envisioned a late stage Horner−Wadsworth−Emmons olefination to install the dienoic side chain (Scheme 3).

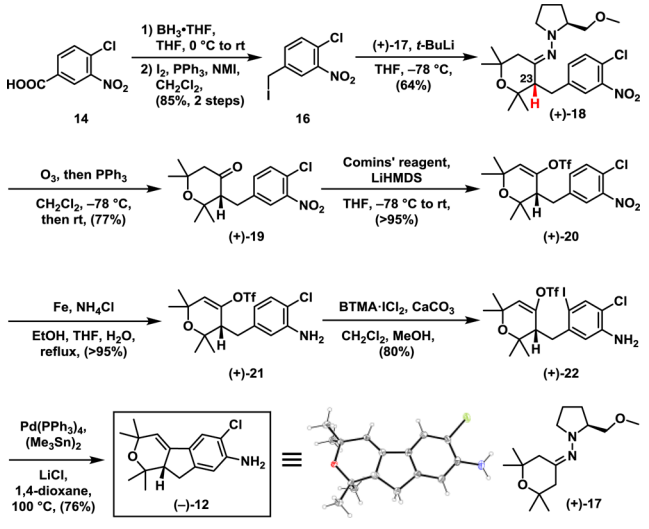
Scheme 3. Retrosynthetic Analysis for (−)-Nodulisporic Acid D (3)



The requisite indole aldehyde **11** would in turn be constructed from two highly functionalized segments, western and eastern hemispheres, chloroaniline **12** and vinyl triflate **13**, respectively. For chloroaniline **12**, an asymmetric alkylation−cyclization sequence, beginning with commercially available 4-chloro-3-nitrobenzoic acid (**14**), would be employed,[4] while the eastern hemisphere, vinyl triflate **13**, would be constructed from unsaturated aldehyde (+)-**15**, prepared via an augmented strategy based on our earlier construction of (+)-nodulisporic acid F (**4**).[14]

We began the synthesis with construction of western hemisphere **12**, employing acid **14** (Scheme 4). Reduction to the corresponding benzyl alcohol (BH_3) and subjection to iodination[15] furnished benzyl iodide **16** in 85% yield for the two steps. Enders alkylation[16] with known hydrazone (+)-**17**[4] next led to (+)-**18** with the requisite S stereogenicity at C(23). Removal of the chiral auxiliary employing ozonolysis generated

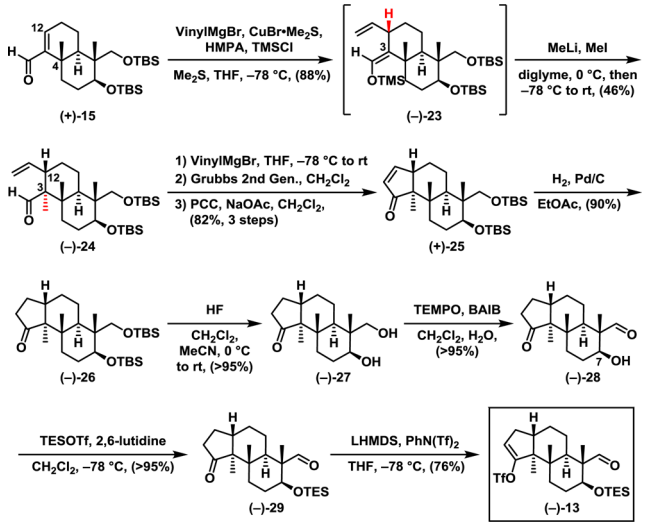
Scheme 4. Synthesis of the Western Hemisphere Subtarget



ketone (+)-**19**, which was readily converted to vinyl triflate (+)-**20** exploiting the Comins reagent.[17] Pleasingly, mild reduction of the nitro group of (+)-**20** promoted by iron/NH_4Cl[18] proceeded in near-quantitative yield. The derived amino triflate (+)-**21** was then subjected to electrophilic iodination[19] to deliver (+)-**22**, which upon Stille−Kelly reaction[20] furnished the western hemisphere (−)-**12**. The structure of (−)-**12** (>95% ee, determined by chiral SFC analysis) was secured by X-ray crystallographic analysis (see Supporting Information). Overall the eight-step sequence proceeded in 25% yield from acid **14**.

To access the eastern hemisphere **13** (Scheme 5), we chose to build on our earlier construction of unsaturated aldehyde

Scheme 5. Synthesis of the Eastern Hemisphere Subtarget



(+)-**15**.[14] Previously, we had employed a Koga tactic[21] to introduce the C(3) stereocenter of (−)-**24**, but reversal of stereogenicity at C(12) resulted, which in turn required a multistep epimerization sequence to correct the stereochemical outcome. Looking for a more direct (i.e., efficient) route to introduce the two critical stereocenters at C(3) and (12), the conjunction points of the trans-fused 5/6-ring system, we turned to a vicinal difunctionalization strategy inspired by the cuprate addition protocol developed by Corey,[22] and employed subsequently by Snider[23] in their synthesis of erinacine A. Given that predicting the stereochemical outcome of such 1,4-additions is often not straightforward,[23] we reasoned that, for (+)-**15**, the cuprate would approach from the *re* face of C(12) due to the steric congestion derived from the C(4) angular methyl group on the *si* face. In situ capture with TMSCl would then furnish the enol silyl ether, which upon generation of the lithium enolate (MeLi) would permit axial methylation. Initial attempts, employing a Gilman cuprate,[24] however proceeded without selectivity. Use of the Normant cuprate[25] on the other hand provided (−)-**23** with modest diastereoselectivity (dr = 3:1). Further experimentation involving different solvent and reaction temperature regimes demonstrated that the initial diastereoselectivity of the vinyl addition at C(12) could be increased to >15:1.

However, during development of the second stage of this bifunctional transformation, we encountered difficulties with the methylation, leading to both poor chemoselectivity (C-alkylation vs O-alkylation, 1:1.3) and diastereoselectivity (dr = 1.4:1).

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Eventually we discovered that solvent effects play a significant role in the alkylation outcome. Utilizing diglyme instead of THF permitted consistent access to the desired methylation product (−)-**24** (dr = 5:1). In the end, excellent stereo- and chemoselectivities were achieved at both C(3) and C(12).

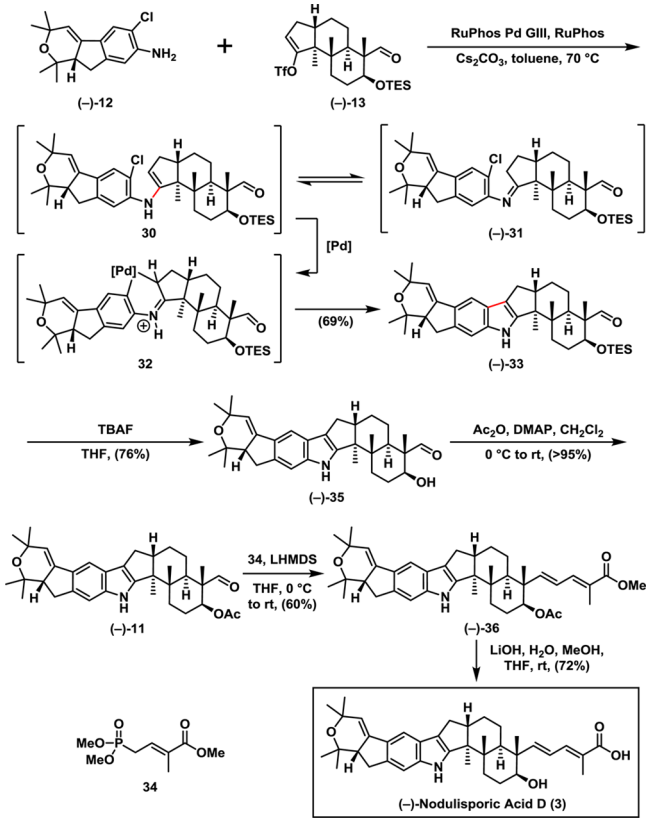
Continuing with the synthesis, a straightforward three-step sequence involving a vinyl Grignard addition, ring-closing metathesis,[26] and PCC oxidation,[27] which together could be achieved without requiring purification, led to (+)-**25**, the requisite trans-fused E,F-5/6 tricyclic core as a single diastereomer. Deprotection ($HF/CH_2Cl_2/MeCN$) of the resultant hydrogenation product (−)-**26** then furnished diol (−)-**27**, which was subjected to TEMPO promoted chemoselective oxidation. Interestingly, the oxidation conditions (i.e., TEMPO, BAIB, CH_2Cl_2 ,or CH_3CN/aqueous pH 7 buffer)[28] led to epimerization at the C(7) position (dr = 1:1), envisioned to occur via an aldol/retro-aldol equilibration sequence. Changing to a biphasic reaction system (CH_2Cl_2/H_2O, 1:1) successfully circumvented this issue. Protection of alcohol (−)-**28** as the corresponding silyl ether (−)-**29**, followed by triflation, then completed construction of (−)-**13**, the eastern hemisphere, in 23% overall yield for the nine steps from (+)-**15**. Importantly, construction of (−)-**13** comprises *a new common advanced intermediate* for the future synthesis of the nodulisporic acids and related diterpene alkaloids.

With the requisite western and eastern hemispheres (−)-**12** and (−)-**13** in hand, we initiated studies on their union employing the earlier developed palladium mediated indolization. Pleasingly the combination of the Buchwald third generation RuPhos precatalyst[29] in conjunction with cesium carbonate, as well as temperature control (70 °C) (Scheme 6), furnished (−)-**33** in 69% yield. Careful analysis of the union reaction sequence revealed that the Buchwald−Hartwig amination proceeded first to form the C−N adduct, which could be isolated as imine (−)-**31**. In situ cyclization then led to the multisubstituted indole (−)-**33**, importantly with the aldehyde intact! Presumably the initial Buchwald−Hartwig coupling leading to enamine **30** undergoes oxidative addition of the C−Cl bond to form an organopalladium species, which we reason can access two pathways to generate the final product: (a) an unusual Heck-type reaction via anti-hydride elimination;[30] or (b) more likely, nucleophilic attack of the described enamine on the palladium center to form a palladacycle (**32**), followed by deprotonation and reductive elimination[31] to furnish the desired indole (−)-**33**.

Having achieved the critical union of (−)-**12** and (−)-**13**, we turned to complete the carbon skeleton of nodulisporic acid D (**3**), namely by introduction of the dienoate side chain. Initially (−)-**33** appeared to be surprisingly inert toward the Horner−Wadsworth−Emmons reaction[32] with the known phosphonate **34**,[33] likely due to the steric congestion present at the aldehyde carbonyl. We were however able to access the requisite dienoate ester (−)-**36** after substituting the TES protecting group for an acetyl. We reason that the acetyl carbonyl group of (−)-**11** may facilitate the required olefination by directing the phosphonate anion. Base hydrolysis then revealed both the secondary hydroxyl and the carboxylic acid groups to provide (−)-nodulisporic acid D (**3**), identical with spectral data[1e] published by the Merck Research Laboratories. Overall the synthesis of (−)-nodulisporic acid D (**3**) proceeded in 5.1% overall yield for the 15 steps from aldehyde (+)-**15**.

In summary, the first total synthesis of (−)-nodulisporic acid D (**3**) has been achieved via a 15-step, longest linear reaction sequence. The key transformations include vicinal difunctionalization of an α,β-unsaturated aldehyde to install stereoselectively the critical C3 and C12 stereogenic centers, and a palladium mediated cross-coupling cascade to generate the substituted indole nucleus from two highly functionalized intermediates. Studies toward the synthesis of (+)-nodulisporic acid A (**1**) continue in our laboratory.

Scheme 6. Cascade Cross-Coupling Union and End-Game Strategy



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, as well as spectroscopic and analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04728.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809. (b) Hensens, O. D.; Ondeyka, J. G.; Dombrowski, A. W.; Ostlind, D. A.; Zink, D. L. *Tetrahedron Lett.* **1999**, *40*, 5455. (c) Ondeyka, J. G.; Dahl-Roshak, A. M.; Tkacz, J. S.; Zink, D. L.; Zakson-Aiken, M.; Shoop, W. L.; Goetz, M. A.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2941. (d) Ondeyka, J. G.; Byrne, K.; Vesey, D.; Zink, D. L.; Shoop, W. L.; Goetz, M. A.; Singh, S. B. *J. Nat. Prod.* **2003**, *66*, 121. (e) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. *J. Nat. Prod.* **2004**, *67*, 1496.

(2) (a) Smith, M. M.; Warren, V. A.; Thomas, B. S.; Brochu, R. M.; Ertel, E. A.; Rohrer, S.; Schaeffer, J.; Schmatz, D.; Petuch, B. R.; Tang, Y. S.; Meinke, P. T.; Kaczorowski, G. J.; Cohen, C. J. *Biochemistry* **2000**, *39*, 5543. (b) Kane, N. S.; Hirschberg, B.; Qian, S.; Hunt, D.; Thomas, B.; Brochu, R.; Ludmerer, S. W.; Zheng, Y.; Smith, M.; Arena, J. P.; Cohen, C. J.; Schmatz, D.; Warmke, J.; Cully, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 13949. (c) Ludmerer, S. W.; Warren, V. A.; Williams, B. S.; Zheng, Y.; Hunt, D. C.; Ayer, M. B.; Wallace, M. A.; Chaudhary, A. G.; Egan, M. A.; Meinke, P. T.; Dean, D. C.; Garcia, M. L.; Cully, D. F.; Smith, M. M. *Biochemistry* **2002**, *41*, 6548.

(3) Meinke, P. T.; Colletti, S. L.; Fisher, M. H.; Wyvratt, M. J.; Shih, T. L.; Ayer, M. B.; Li, C.; Lim, J.; Ok, D.; Salva, S.; Warmke, L. M.; Zakson, M.; Michael, B. F.; de Montigny, P.; Ostlind, D. A.; Fink, D.; Drag, M.; Schmatz, D. M.; Shoop, W. L. *J. Med. Chem.* **2009**, *52*, 3505.

(4) (a) Smith, A. B., III; Ishiyama, H.; Cho, Y. S.; Ohmoto, K. *Org. Lett.* **2001**, *3*, 3967. (b) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971. (c) Smith, A. B., III; Davulcu, A. H.; Kurti, L. *Org. Lett.* **2006**, *8*, 1665.

(5) (a) Liu, C.; Tagami, K.; Minami, A.; Matsumoto, T.; Frisvad, J. C.; Suzuki, H.; Ishikawa, J.; Gomi, K.; Oikawa, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 5748. (b) Tagami, K.; Liu, C.; Minami, A.; Noike, M.; Isaka, T.; Fueki, S.; Shichijo, Y.; Toshima, H.; Gomi, K.; Dairi, T.; Oikawa, H. *J. Am. Chem. Soc.* **2013**, *135*, 1260. (c) Byrne, K. M.; Smith, S. K.; Ondeyka, J. G. *J. Am. Chem. Soc.* **2002**, *124*, 7055.

(6) Smith, A. B., III; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K.; Kuerti, L.; Ishiyama, H. *J. Org. Chem.* **2007**, *72*, 4596.

(7) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757.

(8) Smith, A. B., III; Cui, H. *Helv. Chim. Acta* **2003**, *86*, 3908.

(9) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254.

(10) (a) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem.—Eur. J.* **2005**, *11*, 2276. (b) Barluenga, J.; Valdes, C. *Chem. Commun.* **2005**, 4891.

(11) Smith, A. B.; Kürti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611.

(12) (a) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.

(13) (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(14) Smith, A. B., III; Kurti, L.; Davulcu, A. H.; Cho, Y. S. *Org. Process Res. Dev.* **2007**, *11*, 19.

(15) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

(16) Enders, D.; Zamponi, A.; Raabe, G.; Runsink, J. *Synthesis* **1993**, *1993*, 725.

(17) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(18) Ramadas, K.; Srinivasan, N. *Synth. Commun.* **1992**, *22*, 3189.

(19) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. *Chem. Lett.* **1987**, *16*, 2109.

(20) (a) Ross Kelly, T.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161. (b) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (c) Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55.

(21) (a) Hashimoto, S.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 771. (b) Kogen, H.; Tomioka, K.; Hashimoto, S.-I.; Koga, K. *Tetrahedron* **1981**, *37*, 3951.

(22) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(23) Snider, B. B.; Vo, N. H.; O'Nei, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.

(24) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.

(25) Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, *12*, 2583.

(26) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(27) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(28) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(29) (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916. (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (c) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

(30) (a) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679. (b) Oestreich, M. *The Mizoroki—Heck Reaction*; Wiley: 2009. (c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (d) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

(31) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588.

(32) (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(33) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155.

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