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Catalytic Enantioselective Synthesis of Amino Skipped Diynes

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Supporting Information

ABSTRACT: The Cu-catalyzed synthesis of nonracemic 3-amino skipped diynes via an enantiodetermining C−C bond formation is described using StackPhos as ligand. Despite challenging issues of reactivity and stereoselectivity inherent to these chiral skipped diynes, the reaction tolerates an extremely broad substrate scope with respect to all components and provides the title compounds in excellent enantiomeric excess. The alkyne moieties are demonstrated here to be useful synthetic handles, and 3-amino skipped diynes are convenient building blocks for enantioselective synthesis.

Natural products assembled by biosynthetic pathways involving hybrid polyketide synthase (PKS) and nonribosomal peptide synthetase (NRPS) machinery can possess interesting structures and exhibit potent biological activities.[1] Utilizing a combination of the PKS/NRPS modules permits the direct fusion of polyketides and peptides and also facilitates the construction of heterocycles to yield important classes of compounds such as β-lactams (e.g., nocardicins)[2] and oxazoles (e.g., rhizoxin)[3] among many others.[4] Recently, several linear mono- and polyamines exhibiting broad spectrum antibiotic activity have been isolated including the zeamines,[5] fabclavines,[6] and taveuniamides,[7] but their stereochemistry remains unassigned (Figure 1).

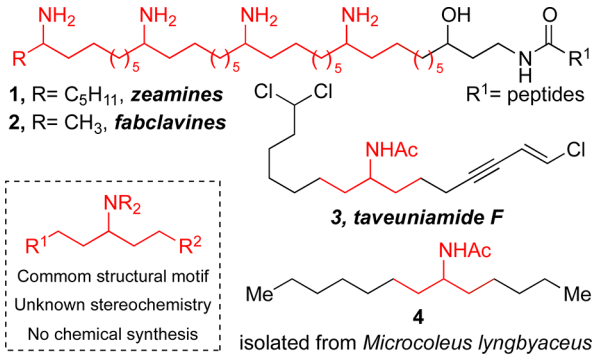

Figure 1. Linear mono- and polyamine natural products.

While nature utilizes hybrid PKS/NRPS assembly lines to iteratively build up these structures by stereoselectively introducing the primary amine moieties with concurrent removal of ancillary functional groups, the enantioselective chemical synthesis of stereocenters bearing two highly similar groups is a formidable challenge complicating the complete structural assignment of these natural products. Chiral, nonracemic amines are exceedingly important compounds that find use in a myriad of research areas and commercial settings.[8] They are often obtained by resolution or chiral auxiliary chemistry,[9] and catalytic enantioselective methods for their preparation have proven challenging,[10] especially when the stereocenter bears two nearly equivalent alkyl groups,[11] as observed in **3** and **4**.[12,13] Recently, very nice examples of enantioselective intermolecular hydroamination have appeared.[14] These reactions employ symmetrical olefin starting materials[12] or directing groups[15] to control regioselectivity. An alternative bond construction would involve C−C bond formation, and we envisioned that this may provide a complementary method with a different substrate scope, facilitating the inclusion of groups such as π-bonds that would be useful for further functionalization. In this vein, we sought to prepare 3-amino-1,4-diynes[16] by acetylide addition for maximal synthetic flexibility in the positions adjoining the stereogenic center. This would be an extremely demanding reaction with respect to both reactivity and stereoselectivity, as many problematic side reactions could be envisioned and the differences between the groups are quite distal from the reaction center with no α-branching to augment selectivity (Figure 2). Herein we report a convergent, highly enantioselective synthesis of versatile, chiral 3-amino skipped diyne building blocks.

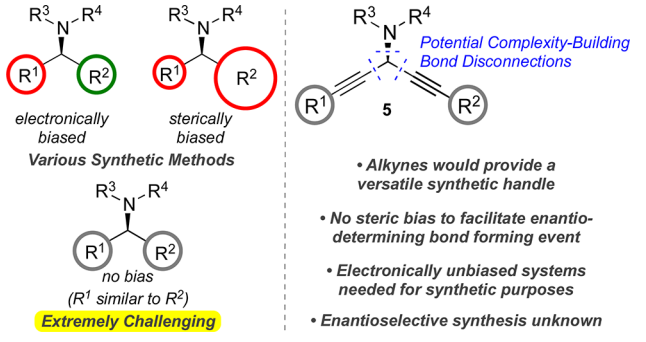

Figure 2. Chiral 3-amino skipped diynes.

At the outset, considering the large body of literature reporting the addition of nucleophiles to imines and iminium ions, the enantioselective synthesis of diynes **5** by C−C bond formation would be problematic.[17] The anticipated difficulties included addition to the highly electrophilic β-position,[18] enamine formation, racemization of the product under the reaction

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conditions through a highly stabilized carbocation,[19] or by the well-known base-catalyzed 1,4-diyne/1-allen-4-yne equilibrium.[20] In the racemic sense, the reactivity problems were overcome by generating the electrophile by ionization of N,X-acetals;[21] however, few examples incorporate two different alkyne moieties, and the stoichiometric activators employed would likely racemize the products of an enantioselective variant. We surmised that all of these issues could be overcome if a catalytic enantioselective reaction employing extremely mild conditions could be developed.

To test this hypothesis, ynal **6a**, dibenzylamine **7a**, and TMS-acetylene **8a** were allowed to react in toluene at 0 °C for 24 h in the presence of 5 mol % of CuBr and 5.5 mol % *rac*-StackPhos.[22] Under these conditions, the diyne **9a** was isolated in 20% yield, and the remainder of the material was unreacted aldehyde (Table 1, entry 1). This result demonstrated the desired reactivity, but

Table 1. Optimization Studies

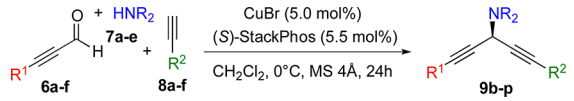
entry[a]	solvent	temp (°C)	yield (%)	ee (%)
1[b]	PhMe	0	20	–
2[b]	CH_2Cl_2	0	94	–
3[c]	CH_2Cl_2	0	5	–
4[d]	CH_2Cl_2	0	73	95
5[d]	CH_2Cl_2	rt	85	94

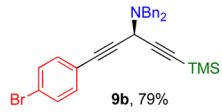
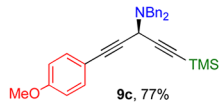
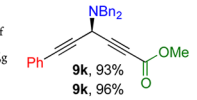
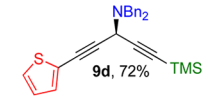
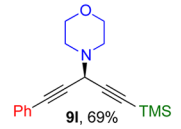
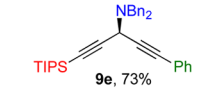
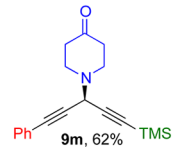
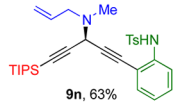
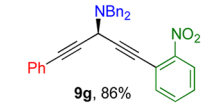
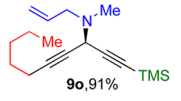
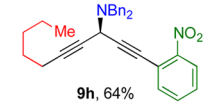
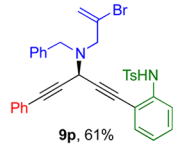
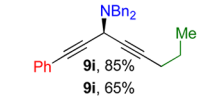
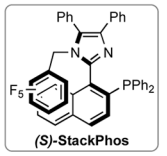
[a]CuBr (5.0 mol %), ligand (5.5 mol %). [b]*rac*-StackPhos. [c]Without ligand. [d]Ligand = (*S*)-StackPhos (99% ee).

substantial optimization was needed. Employing dichloromethane as solvent, the yield improved to 94% (entry 2). A control reaction without ligand furnished only trace amount of product (entry 3), and with 99% ee (*S*)-StackPhos, **9a** was isolated in 73% yield and 95% ee (entry 4). The yield improved to 85% at ambient temperature, and under these conditions **9a** was isolated in 94% ee (entry 5), effectively demonstrating that the products could be obtained in both high chemical and optical yields.[23]

With optimal conditions established, the scope of the reaction was studied, and it was found that this enantioselective transformation is versatile and robust, tolerating different aldehydes, alkynes, and amines. The aromatic group could be substituted (Table 2, entries 1, 2) or be heteroaromatic (entry 3), leading to products in 96%, 94%, and 96% ee, respectively. Reversing the position of the silyl and aryl groups led to the preparation of compound **9e** in 95% ee (entry 4). After desilylation **9a** and **9e** are enantiomers, although both were formed using the same enantiomer of the ligand.[24] Two silyl groups or two aromatics could be incorporated (entries 5, 6), aliphatic groups were also well tolerated on both reaction components (entries 7–10), and propiolates proved to be most reactive, generating the unsaturated GABA analogue **9k**[25] in 1 h (entries 11, 12), all forming products in high ee's. Remarkably, changing the alkyne substituents results in only small changes in enantioselectivity. It is possible that having two similar groups may present general practical difficulties for forming stereocenters; but here, since the structural permutations are remote, the scope can be greatly expanded due to spatially diminished steric and electronic perturbations.

Table 2. Reaction Scope Studies



entry	product, yield	ee[a] (%)	entry	product, yield	ee[a] (%)
1[b]	 **9b**, 79%	96	10[d]	 **9j**, 86%	82
2	 **9c**, 77%	94	11[f]	 **9k**, 93%	82
			12[f,g]	**9k**, 96%	86
3	 **9d**, 72%	96[c]	13	 **9l**, 69%	95
4	 **9e**, 73%	95	14	 **9m**, 62%	90
5	 **9f**, 72%	96[c]	15[d]	 **9n**, 63%	90
6[d]	 **9g**, 86%	95	16[d]	 **9o**, 91%	95[h]
7[d]	 **9h**, 64%	96	17[d]	 **9p**, 61%	84
8[d]	 **9i**, 85%	86		 (*S*)-StackPhos	
9[e,f]	**9i**, 65%	89			

[a]Determined by chiral HPLC. [b]Absolute stereochemistry determined by X-ray crystallography; see SI for full details. [c]Determined after desilylation. [d]Reaction time = 3 h. [e]Reaction time = 6 h. [f]Reaction time = 1 h. [g]Reaction temp = −25 °C. [h]Determined after Pauson–Khand reaction (Scheme 2).

The aforementioned examples all employed dibenzylamine, but it would be synthetically useful to incorporate other secondary amines, especially compounds with two different amine substituents. To evaluate the reaction scope to this end, morpholine, piperidone, and amines with different substituents were used. With the symmetric amines, **9l** and **9m** were isolated in 95% and 90% ee, respectively (entries 13, 14). More challenging, unsymmetrical secondary amines could also be employed in highly enantioselective reactions (entries 15–17), which is exceptionally uncommon and extremely useful.[17]

As described above, the substrate scope is broad and tolerates different reaction partners by essentially exchanging the groups on the alkyne. This offers flexibility in much the same way as cross coupling reactions, where the halide and organometallic

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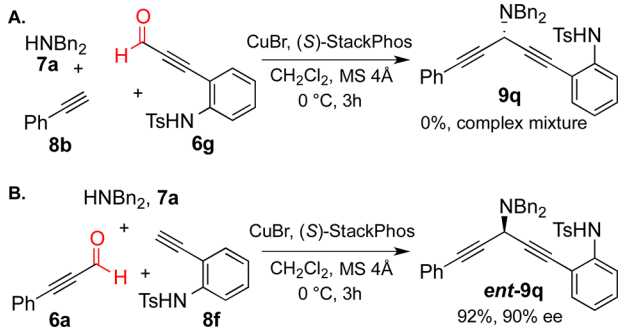
can be interchanged to produce a new pair of reactants.[26] During studies on the reaction scope, it was observed that synthesis of **9q** completely failed when the ynal was *o*-substituted with a sulfonamide moiety (Scheme 1A). Reaction of **6g** with

Scheme 1. Alternative Reaction Partners



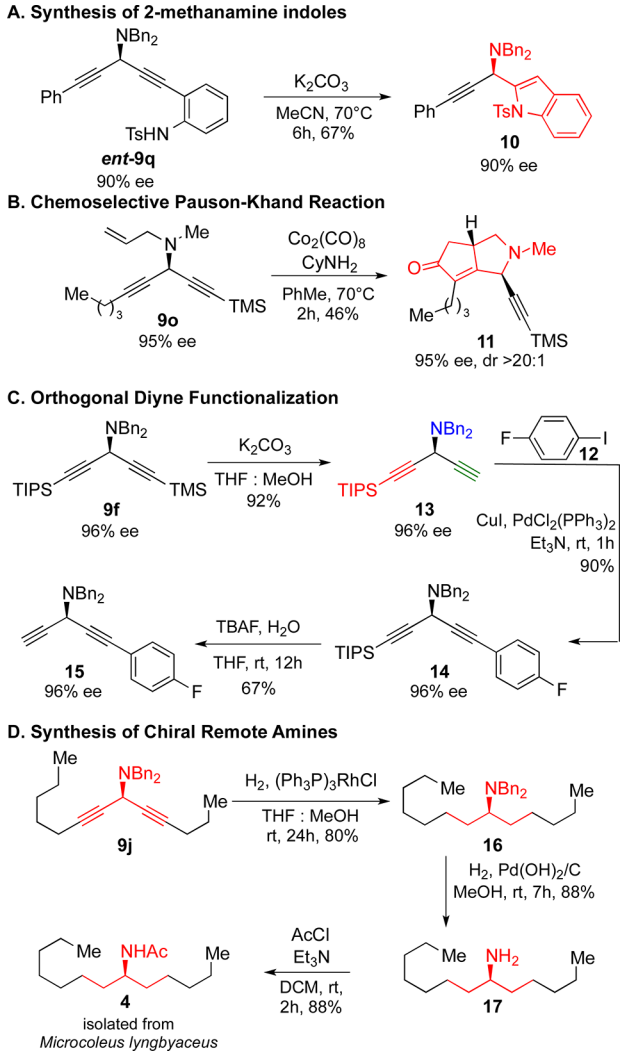
dibenzylamine and phenylacetylene under the standard conditions resulted in an intractable mixture, as the aldehyde appears unstable to the reaction conditions.[27] However, if the alkyne substituents are exchanged, the reaction proceeds smoothly, delivering ***ent*-9q**, in 92% yield and 90% ee (Scheme 1B). Although this alternative substrate pair leads to the enantiomeric product, this is not limiting as both enantiomers of the ligand are available.[22]

The newly synthesized amines offer many positions for further functionalization and should be highly useful synthons. Examples of the synthetic utility are included in Scheme 2. The 2-substituted indole **10** was prepared via hydroamination of ***ent*-9q** using K_2CO_3 without loss of ee (Scheme 2A). Nonracemic C2-methanamine-substituted indole is an important natural product motif[28] that is found in lead compounds broadly utilized in medicinal chemistry,[29] but these compounds are difficult to prepare without C3 substituents.[30] The substituents on the nitrogen can also be utilized, which is especially useful when two different groups are present. Chemoselective Pauson–Khand reaction of **9o** generates the heterocycle **11** as a single diastereomer (Scheme 2B).[31] The *N*-allyl group reacts preferentially with the alkyl-substituted alkyne, and no reaction involving the silyl substituted alkyne is observed. The silyl substituents can be removed, and different substituents appended, although broad substrate scope may preclude the need for this (Scheme 2C). The amine **9f** was desilylated to form **13**, a potential building block for diversity-oriented synthesis,[32] and **15** after further functionalization.[33]

Additionally, the simple natural product **4**[34] (Figure 1), which was isolated from marine cyanobacteria *Microcoleus lyngbyaceus*,[34] was prepared in a straightforward manner. Starting from diyne **9j**, **16** and **17** were prepared after simple reduction of the acetylenes using Wilkinson's catalyst and cleavage of the benzyl groups (Scheme 2D). The free amine **17** was then acylated to complete the synthesis of **4**. To date, none of the taveuniamides have been prepared in enantioenriched form, but these and the polyamines should be accessible using this methodology to establish the challenging stereocenters.

In summary, we have disclosed the first enantioselective preparation of amino skipped diynes, a class of chiral molecules with minimal differences in two of the substituents rendering them chiral. Despite this challenging issue and potential reactivity issues, a Cu(I)-StackPhos-catalyzed C–C bond formation proved to be rapid and high yielding under very mild conditions

Scheme 2. Versatility of 3-Amino Skipped Diynes



while tolerating an exceptionally broad substrate scope. Due to the unique structural features of chiral 3-amino skipped diynes, we believe these building blocks will find application in a variety of areas, and to this end, we have demonstrated several preliminary applications. The method should enable the synthesis of more complex primary amine and polyamine natural products. These studies as well as detailed mechanistic investigations are ongoing in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13387.

Experimental details and data (PDF)
Crystallographic data for ***ent*-9b** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Fisch, K. M. *RSC Adv.* **2013**, *3*, 18228. Boettger, D.; Hertweck, C. *ChemBioChem* **2013**, *14*, 28.
(2) Gaudelli, N. M.; Long, D. H.; Townsend, C. A. *Nature* **2015**, *520*, 383.
(3) (a) Partida-Martinez, L. P.; Hertweck, C. *Nature* **2005**, *437*, 884. (b) Partida-Martinez, L. P.; Hertweck, C. *ChemBioChem* **2007**, *8*, 41.
(4) Pang, B.; Wang, M.; Liu, W. *Nat. Prod. Rep.* **2016**, *33*, 162.
(5) Wu, J.; Zhang, H.-B.; Xu, J.-L.; Cox, R. J.; Simpson, T. J.; Zhang, L.-H. *Chem. Commun.* **2010**, *46*, 333.
(6) Fuchs, S. W.; Grundmann, F.; Kurz, M.; Kaiser, M.; Bode, H. B. *ChemBioChem* **2014**, *15*, 512.
(7) (a) Tan, L. T. *Phytochemistry* **2007**, *68*, 954. (b) Williamson, R. T.; Singh, I. P.; Gerwick, W. H. *Tetrahedron* **2004**, *60*, 7025.
(8) For chiral amines in pharmaceuticals see: (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348. In natural products: (b) Fattorusso, E.; Taglialatela-Scafati, O. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Wiley: Hoboken, NJ, 2008. In catalysis: (c) Zhou, Q.-L. *Privileged Chiral Ligands and Catalysts*; Wiley: Hoboken, NJ, 2011. (d) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 1999. In materials science and polymers: (e) Yashima, E.; Maeda, K. *Macromolecules* **2008**, *41*, 3. Levine, M.; Kenesky, C. S.; Zheng, S.; Quinn, J.; Breslow, R. *Tetrahedron Lett.* **2008**, *49*, 5746. In bioconjugates: (f) Romanini, D. W.; Francis, M. B. *Bioconjugate Chem.* **2008**, *19*, 153. (g) Morales, A. R.; Schafer-Hales, K. J.; Marcus, A. I.; Belfield, K. D. *Bioconjugate Chem.* **2008**, *19*, 2559.
(9) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.
(10) (a) *Stereoselective Formation of Amines*; Li, W., Zhang, X., Eds.; Springer-Verlag: Berlin, 2014. (b) *Chiral Amine Synthesis: Methods, Developments, and Applications*; Nugent, T. C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2010.
(11) The catalytic enantioselective synthesis of diarylmethylamines has been extensively explored. For a review see: (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. For recent leading references see: (b) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344. (c) Zhao, G.-Z.; Sipos, G.; Salvador, A.; Ou, A.; Gao, P.; Skelton, B. W.; Dorta, R. *Adv. Synth. Catal.* DOI: 10.1002/adsc.201500975 and references cited therein.
(12) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.
(13) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.
(14) Pirnot, M. T.; Wang, M.-T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 48.
(15) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 776.
(16) Enantioselective preparation of skipped diynes is scarce: (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (b) Tedeschi, C.; Saccavini, C.; Maurette, L.; Soleilhavoup, M.; Chauvin, R. *J. Organomet. Chem.* **2003**, *670*, 151.
(17) (a) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626. (b) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790. (c) Zhao, C.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 4650. (d) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437. (e) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.
(18) (a) Zhou, L.; Jiang, H.-F.; Li, C.-J. *Adv. Synth. Catal.* **2008**, *350*, 2226. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (d) Knopfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054.
(19) Naredla, R. R.; Klumpp, D. A. *Chem. Rev.* **2013**, *113*, 6905.
(20) (a) Mathai, I. M.; Taniguchi, H.; Miller, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 115. (b) Gensler, W. J.; Casella, J., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 1376.
(21) For racemic synthesis of 3-amino skipped diynes see: (a) Gommermann, N.; Koradin, C.; Knochel, P. *Synthesis* **2002**, *14*, 2143. (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (c) Korbad, B. L.; Lee, S.-H. *Eur. J. Org. Chem.* **2014**, *2014*, 5089. Yao, B.; Zhang, Y.; Li, Y. *J. Org. Chem.* **2010**, *75*, 4554.
(22) (a) Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548. (b) Pappoppula, M.; Cardoso, F. S. P.; Garrett, B. O.; Aponick, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15202. (c) Pappoppula, M.; Aponick, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15827.
(23) Differences in reactivity are observed when *rac*-ligand is employed. The mechanistic underpinnings for this are under investigation and will be reported in due course. See Supporting Information for further details.
(24) (a) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. A. *Chem. Commun.* **2005**, *19*, 2512. Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444.
(25) (a) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (b) Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281.
(26) Prieto, M.; Zurita, E.; Rosa, E.; Munoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2004**, *69*, 6812.
(27) (a) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gomez-Bengoa, E.; Garcia, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188. (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126.
(28) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.
(29) (a) Yoshihiro, B.; Ryoma, H.; Ryosuke, T. WO2009110520, September 11, 2009. (b) Gurmit, G.; Vibbha, O. WO2008059238, May 22, 2008.
(30) (a) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 7052. (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (d) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
(31) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. - Eur. J.* **2003**, *9*, 2797.
(32) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
(33) (a) Beal, D. M.; Jones, L. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6320. (b) Yin, H.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4130.
(34) (a) Tan, L. T. *Phytochemistry* **2007**, *68*, 954. (b) Orsini, M. A.; Pannell, L. K.; Erickson, K. L. *J. Nat. Prod.* **2001**, *64*, 572.

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