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Diastereoselection in the Formation of Contiguous Quaternary Carbon Stereocenters by the Intramolecular Heck Reaction

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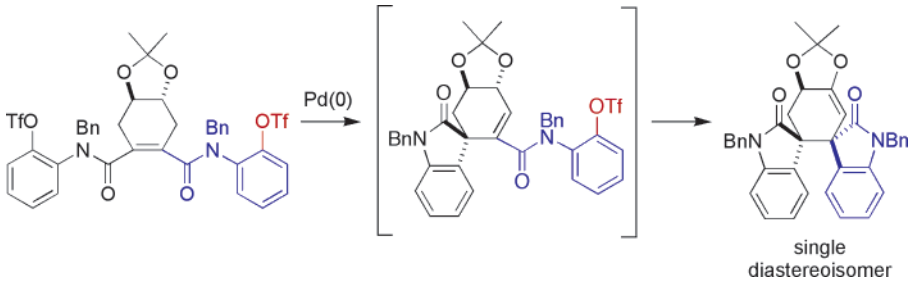
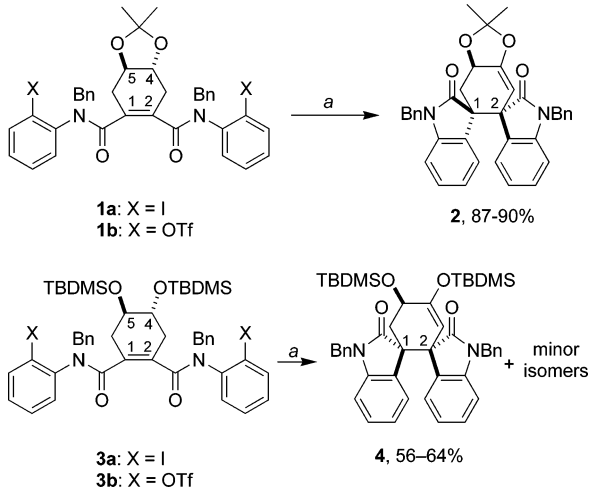


The second in a series of two papers, this study examines the origins of diastereoselection in the second ring closure of the highly diastereoselective double Heck cyclization of cyclohexenes **1** and **3** that form contiguous quaternary stereocenters. Seven model substrates were synthesized and cyclized to examine the structural features responsible for imparting diastereoselection in the second intramolecular Heck reaction. These studies demonstrate that stereoselection in the formation of the second spirooxindole ring results from the avoidance of steric interactions in the insertion step with the spirooxindole formed in the first Heck cyclization. An axial substituent (carbonyl or arene) is required at the allylic position for high levels of diastereoselection to be realized.

Introduction

In the context of recent total syntheses of *meso*- and (−)-chimonanthine, we described the sequential double Heck cyclization of C_2-symmetric diiodides **1a** and **3a**.[1] These reactions, as well as those of the related ditriflate **1b** or **3b**,[2] provided spirocyclic dioxindoles **2** and **4** with high levels of diastereoselection (Scheme 1). Depending upon the nature of the diol protecting group, the new spirocyclic oxindoles were formed with either a trans or a cis stereorelationship. Double Heck cyclizations of acetonides **1a** and **1b** were particularly stereoselective, providing trans-hexacyclic dioxindole **2** as a single detectable stereoisomer. The identical reaction of disiloxy substrates **3** produced as the major product pentacyclic dioxindole **4** having the alternative cis relationship of the newly formed oxindole groups, although this transformation was less clean than that of acetonide congeners **1**. These reactions are notable for their ability to stereoselectively form vicinal quaternary carbon stereocenters, a challenging structural feature that can be constructed by few extant synthetic methods.[3]

SCHEME 1[a]



[a] Key: (a) 20 mol % $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 24 h.

As a result of the synthetic utility of the transformations depicted in Scheme 1, we wished to further understand the factors that control diastereoselection in these sequences. Studies

(1) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7003.
(2) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587−2599.

10.1021/jo0523363 CCC: $33.50
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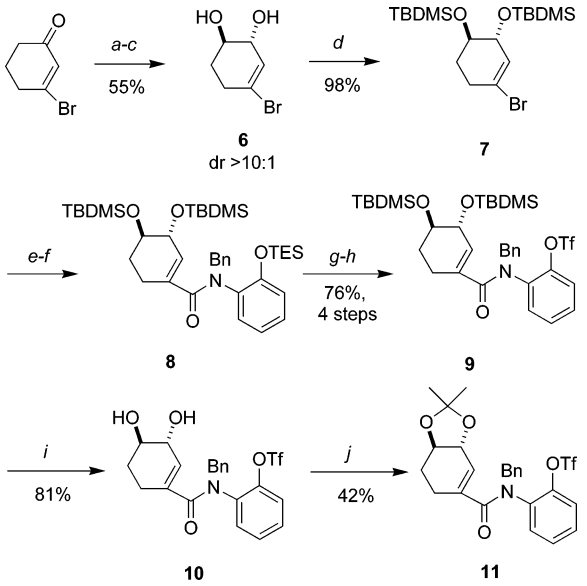
SCHEME 2[a]

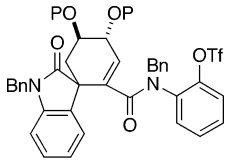


[a] Key: (a) TMSOTf, Et_3N; (b) *m*-CPBA, then HCl; (c) $NaBH(OAc)_3$; (d) TBDMSOTf, 2,6-lutidine; (e) *t*-BuLi, then CO_2; (f) *N*-benzyl-*2*-(triethylsiloxy)aniline, Mukaiyama's salt, 2,4,6-collidine; (g) K_2CO_3, H_2O; (h) $PhNTf_2$, Cs_2CO_3; (i) aq HF; (j) 1 equiv 2,2-DMP, 10 mol % PPTS, 4 Å MS, PhH, 80 °C.

reported in the preceding paper examined the origin of diastereoselection in the first Heck cyclization step.[2] This report describes our studies into the origin of stereoselection in the second ring-closing event of these unique transformations.

Results

Our strategy was to examine this second Heck cyclization with substrates that contained various structural components of the initially formed spirooxindole intermediates **5** generated upon the Heck reaction of ditriflates **1** and **3**. The stereocontrol imparted by the protected *trans*-diol and spirooxindole structural fragments would be explored.



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Synthesis of Heck Cyclization Substrates. The syntheses of cyclization substrates **9** and **11**, that contain the protected diol unit but lack the spirooxindole fragment, are summarized in Scheme 2. These preparations start with 3-bromocyclohexenone,[4] which was converted to the corresponding 2-siloxy-1,3-diene by a reaction with TMSCl and Et_3N. Rubottom oxidation of this intermediate,[5] followed by stereoselective reduction of the resultant α-hydroxyketone with $NaHB(OAc)_3$,[6] provided *trans*-diol **6** with greater than 10:1 diastereoselectivity. Recrystallization of this material provided diastereomerically pure diol **6** in 55% yield over the three steps.[7] Silylation of **6** with TBDMSOTf and 2,6-lutidine gave disiloxy bromide **7** in 98% yield. Although palladium-catalyzed carbonylation of this intermediate was unsuccessful,[8] lithium/bromine exchange using *t*-BuLi and quenching of the resultant vinyllithium intermediate with CO_2 provided the corresponding acid in good yield. Coupling of this acid with *N*-benzyl-*2*-(triethylsiloxy)aniline using *N*-methyl-2-chloropyridium iodide (Mukaiyama's salt)[9] provided disiloxy anilide **8**. Removal of the triethyl silane protecting group from this coupled product, followed by triflation of the resulting phenol, provided disiloxy triflate **9** in 76% overall yield from diol alkenyl bromide **6**.

The corresponding acetonide **11** precursor was accessed from disiloxy triflate **9**. The silyl protecting groups were removed by the reaction of **9** with aqueous hydrofluoric acid to provide diol **10**. The use of other fluoride sources, such as Bu_4NF, resulted in slower deprotection at room temperature and sporadically led to triflate cleavage, even when the reaction was buffered with acetic acid. The conversion of diol **10** to acetonide **11** proved surprisingly challenging. Subjection of diol **10** to various conditions commonly used to form acetonides failed to generate acetonide **11**.[10] Similar difficulties have been described in the conversion of *trans*-diol **6** to its acetonide derivative.[7] Conditions were finally developed to carry out this transformation, albeit in moderate yield: the reaction of diol **10** with 1 equiv of 2,2-dimethoxypropane (2,2-DMP), catalytic pyridinium *p*-toluenesulfonate (PPTS), and 4 Å molecular sieves (4 Å MS) in benzene at 80 °C provided acetonide **11** in 42% yield.[11] Presumably, the removal of methanol from the reaction media by the molecular sieves facilitates formation of the otherwise thermodynamically disfavored acetonide **11**.[12]

The preparations of cyclization substrates **17a**, **17b**, **21a**, and **21b**, which contain a spirooxindole substituent, are summarized in Schemes 3 and 4. Methyl ester **12**[2] was investigated initially as a starting material for preparing triflatoanilide **17a** (Scheme 3). However, attempts to cleave this ester under a variety of conditions (LiOH in THF/H_2O, KOTMS in Et_2O,[13] "anhydrous hydroxide",[14] LiCl or LiI in pyridine,[15] $(Bu_3Sn)_2O$,[16] and several

(3) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943−11948.

(4) Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210−223.

(5) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319−4322.

(6) For leading references to hydroxy-directed reductions of ketones, see: Gribble, G. W. Sodium Triacetoxyborohydride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley & Sons: New York, 1995; Vol. 7, pp 4649−4653.

(7) For a previous synthesis of this intermediate, see: Banwell, M. G.; Lambert, J. N.; Richards, S. L. *Aust. J. Chem.* **1991**, *44*, 939−950.

(8) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *37*, 3931−3934.

(9) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163−1166.

(10) (a) Cai, J.; Davison, B. E.; Ganellin, C. R.; Thaisrivongs, S. *Tetrahedron Lett.* **1995**, *36*, 6535−6536. (b) Larson, G. L.; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935−3936. (c) Rollin, P.; Pougny, J. R. *Tetrahedron* **1986**, *42*, 3479−3490. (d) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

(11) Heating was required for this transformation; at room temperature, only mono- and diprotected mixed methoxy ketals were isolated for this class of diols.

(12) The acetonide of bromide **5** could also be prepared using this method in 67% yield. For details, see: Watson, D. A. Investigation into the Origins of Diastereoselection in Spirocyclic Oxindole Forming Intramolecular Heck Cyclizations. Ph.D. Thesis, University of California−Irvine, Irvine, CA, 2004.

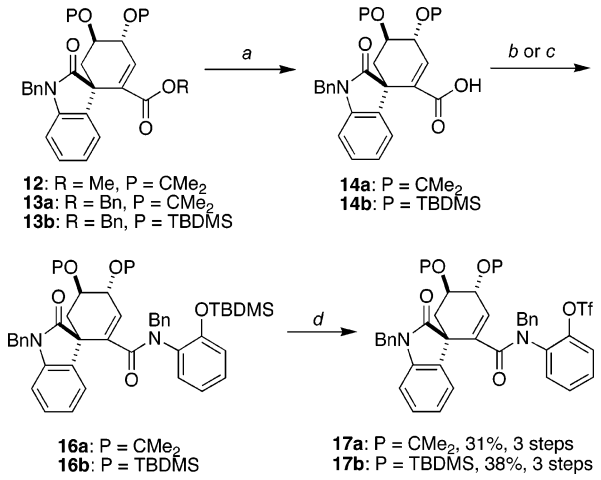
(13) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.

(14) Gassman, P. G.; Schenck, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.

(15) (a) Liotta, C.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, *18*, 4365−4368. (b) Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505−2508.

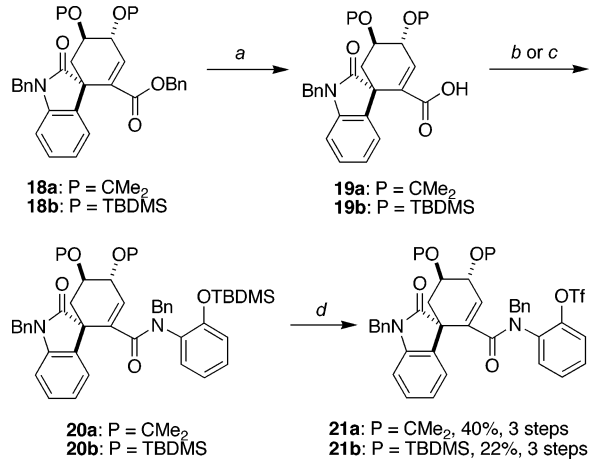
(16) Salomon, C. J.; Mata, E. G.; Mascartti, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239−4242.

SCHEME 3[a]



[a] Key: (a) H_2, Pd/C, EtOAc; (b) $(COCl)_2$, 2,6-lutidine, then **15**; (c) **15**, BOP−Cl, *i*-Pr_2NEt; (d) CsF, Cs_2CO_3, $PhNTf_2$.

SCHEME 4[a]



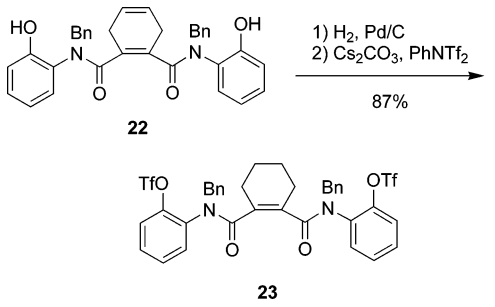
[a] Key: (a) H_2, Pd/C, EtOAc; (b) $(COCl)_2$, 2,6-lutidine, then **15**; (c) **15**, BOP−Cl, *i*-Pr_2NEt; (d) CsF, Cs_2CO_3, $PhNTf_2$.

lipase/esterase conditions[17]) failed to provide the required acid **14a**. These reactions either returned the starting ester or resulted in the decomposition of the substrate. In particular, basic conditions resulted in the rapid decomposition of ester **12**, presumably because of the acidity of the γ methine hydrogen atom. Metal-mediated amidation conditions were also examined. Both aluminum and bromomagenesium amides, generated by the reaction of a variety of primary and secondary anilines with Me_3Al[18] or *i*-PrMgBr,[19] were investigated; however, only the decomposition of the ester was observed. Similar results were observed with the disiloxy congener of **12**, as well as with methyl esters having an epimeric spirooxindole fragment. However, the benzyl ester analogue **13a** cleanly provided the desired acid **14a** when subjected to mild hydrogenolysis conditions.[20,21] Acid **14a** was transformed to the corresponding acyl chloride, coupled with *N*-benzyl-2-(*tert*-butyldimethylsiloxy)aniline (**15**), and the triflate functionality was installed by the reaction of the unsaturated amide product with CsF, Cs_2CO_3, and $PhNTf_2$ to provide triflatoanilide **17a** in 31% overall yield from ester **13a**.

The analogous silyl-protected Heck cyclization substrate **17b** was prepared by a similar sequence (Scheme 3). Hydrogenolysis of disiloxy benzyl ester **13b** readily generated acid **14b**. However, amidation of this acid proved more difficult than in the acetonide series. Attempts to access the corresponding acid chloride by the treatment of this siloxy acid with oxalyl chloride, resulted in a complex mixture of products. When this reaction was carried out in the presence of various anilines, only trace amounts of the desired unsaturated anilide were observed. The use of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate[22] or PyBrOP[23] also failed to provide the coupled product. Likewise, the acyl fluoride derivative of acid **14b**, prepared using $FC(NMe_2)_2PF_6$,[24] failed to react with aniline nucleophiles. Formation of the acyl chloride derivative of **14b** in situ by a reaction with CCl_4 and Ph_3P (in solution or polymer bound) and a reaction at 60 °C with aniline **15** delivered the coupled anilide in ∼20−25% yield.[25] However, unidentified higher molecular weight side products were formed also, requiring preparative HPLC purification to obtain pure samples of anilide **16b**. On the other hand, coupling of disiloxy acid **14b** with aniline **15** in MeCN using bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP−Cl)[26] was cleaner, with only simple column chromatography required to obtain pure samples of anilide **16b**. The conversion of this product to the triflate derivative was straightforward, delivering disiloxy triflate **17b** in 38% yield over the three steps.

The epimeric acetonide- and disiloxy-protected Heck cyclization precursors **21a** and **21b** were prepared from the epimeric benzyl esters **18a** and **18b**[20] using an analogous sequence of reactions (Scheme 4).

Ditriflate **23**, which lacks oxygen substituents at C4 and C5, was synthesized from the Diels−Alder product **22**[27] (eq 1). The regioselective hydrogenation of diene **22** was accomplished by a brief exposure to hydrogen over Pd/C. A reaction of the resultant diphenol with $PhNTf_2$ in the presence of Cs_2CO_3 provided ditriflate **23** in 87% overall yield.



(1)

Heck Cyclizations. This series of unsaturated triflates was cyclized under identical reaction conditions: 20 mol % Pd-

(17) For leading references on the enzymatic cleavage of methyl esters, see: Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley and Sons: New York, 1999; p 385.

(18) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171−4174.

(19) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

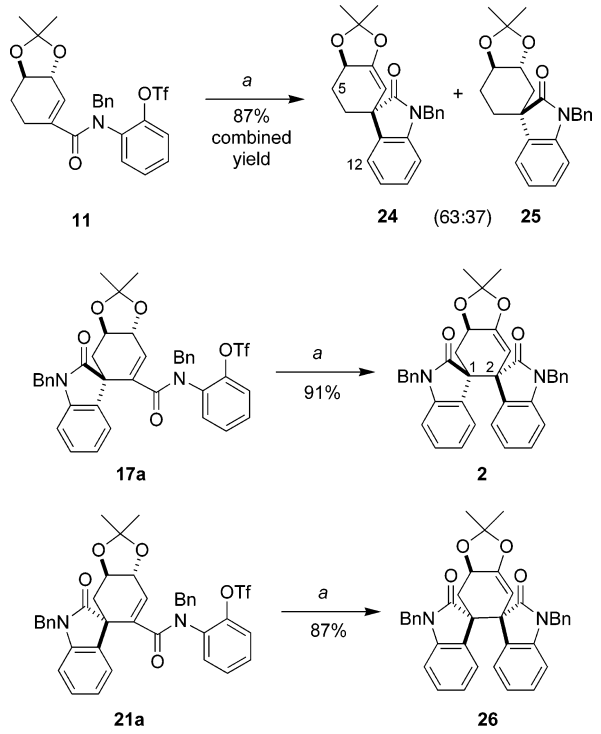
(20) Benzyl esters **13a**, **13b**, **18a**, and **18b** were prepared in analogous fashion to their methyl ester congeners. See ref 2 and Supporting Information for details.

(21) Hydrogenation of the alkene was not observed in this transformation after short reaction times.

(22) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(23) Costa, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967−1970.

SCHEME 5[a]



[a] Key: (a) 20 mol % $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 24 h.

$(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 24 h; product ratios were determined by the analysis of the ^1H NMR spectra of unpurified reaction mixtures. The results of the Heck cyclizations of triflates **11**, **17a**, and **21a**, containing acetonide units, are shown in Scheme 5. In all three cyclizations, the relative configuration of the newly formed spirooxindole (relative to the acetonide) of the major product is the same as that of the second spirooxindole produced in the double cyclization of ditriflate **1b** (Scheme 1).

Heck cyclization of triflate **11**, which lacks an oxindole fragment, provided spirooxindoles **24** and **25** in a 63:37 ratio. These products, which differ in molecular weight by 2 mass units and are epimeric at the quaternary stereocenter, were isolated in 87% combined yield. The configuration of major product **24** was assigned by the observation of a 3.4% NOE enhancement for the C12 hydrogen atom upon irradiation of the axial C5 hydrogen atom.[28] The equatorial disposition of the aryl moiety of the spirooxindole group of minor product **25** was assigned by the observation of NOE enhancements for both the axial C6 and the axial C2 hydrogen atoms upon irradiation of the C12 hydrogen atom.[28] The dihydro product **25** is undoubtedly formed because migratory insertion into the alkene face cis to the proximal ether generates a cyclohexyl palladium species lacking a β-hydrogen atom cis to the metal center. The reduction of this intermediate, most likely by excess Et_3N present in solution, would lead to the cyclohexyl product **25**.

In contrast, triflate **17a**, which contains a spirooxindole unit, cyclized cleanly to provide dioxindole **2** as the only detectable product (by ^1H NMR analysis). This outcome was expected, as spirooxindole **17a** is the putative intermediate in the high-yielding conversion of ditriflate **1b** to dioxindole **2** (Scheme 1). The relative configuration of dioxindole **2** is known from X-ray crystallographic analysis.[1]

Heck cyclization of epimeric oxindole triflate **21a** occurred also with a high degree of diastereoselection, with dioxindole **26** (isolated in 87% yield) being formed as the predominant product together with traces (~3−4%) of an unidentified side product.[29] The relative configuration of Heck product **26** was assigned by chemical correlation: the reaction of this product with dilute aqueous trifluoroacetic acid in refluxing THF cleaved the isopropylidene fragment to provide the corresponding keto alcohol, which had been characterized previously by X-ray crystallographic analysis.[27]

The analogous silyl-protected substrates provided qualitatively similar results upon Heck cyclization (Scheme 6). For example, triflate **9** provided spirooxindoles **27** and **28** in a 57:43 ratio upon Heck cyclization. These products were isolated in 91% combined yield, and their configurations were assigned by NOE analysis. The major product **27**, which adopts a half-chair conformation having the C4 siloxy substituent pseudoaxial (J_{H-H}),[28] displayed a 2.9% NOE for the C12 hydrogen atom upon irradiation of the pseudoaxial hydrogen atom at C6. The minor product **28**, which lacked the siloxy group at C3, displayed a 1.5% NOE enhancement for the C12 hydrogen atom and a 1.9% NOE enhancement for the pseudoaxial C4 methine hydrogen atom upon irradiation of the pseudoaxial hydrogen atom at C6. Spirooxindole **28** arises from the migratory insertion to the alkene face of **9** cis to the proximal siloxy substituent. As the resultant cyclohexyl palladium intermediate lacks a cis β-hydrogen atom, β-siloxy elimination takes place.[30]

Spirooxindole **21b**, which was the putative intermediate en route to the major dioxindole product **4** in the double cyclization of disiloxy ditriflate **3**, underwent Heck cyclization to provide products **4**, **29**, and **30** in a 75:9:16 ratio (Scheme 6).[31,32] The known cis dispirooxindole **4**[2] was isolated in a 52% yield. Arene **30**,[2] which is the product of triflate reduction, was isolated in a 14% yield. The ^1H and ^{13}C NMR spectra of the minor product **29** showed that it had C_2 symmetry. Its relative configuration was established by an independent synthesis by silyl protection of a sample of the corresponding diol.[33] Thus, facial selectivity in the Heck cyclization of siloxy ditriflate **21b** is 89:11. Product **29** arises from a reductive process analogous to that involved

(24) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401−5402.

(25) Lee, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3440−3441.

(26) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547−551.

(27) Stearns, B. A. A Formal Synthesis of Loracarbef and Total Synthesis of Polypyrrolidinoindoline Alkaloids. Ph.D. Thesis, University of California−Irvine, Irvine, CA, 2000.

(28) See Supporting Information for details.

(29) The low yield of this minor product, and the limited amounts of starting material available, prevented successful isolation.

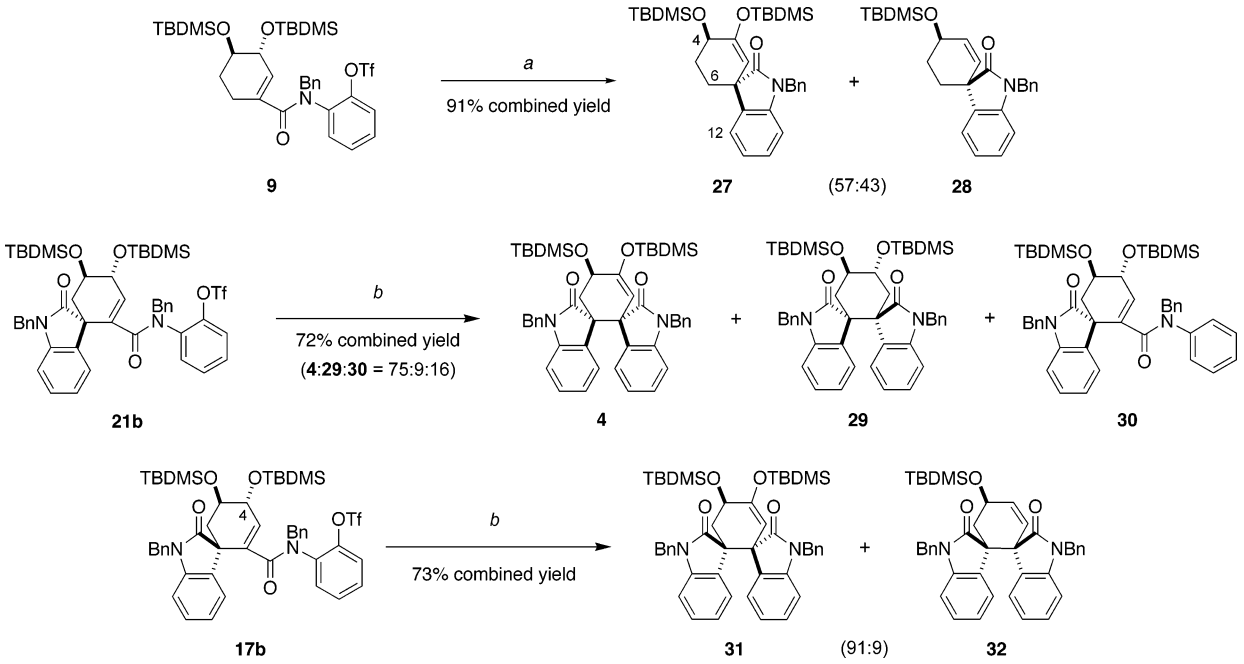
(30) For examples of palladium-mediated reactions terminated by β-alkoxide eliminations, see: (a) Hacksell, U.; Daves, G. D., Jr. *Organometallics* **1983**, *2*, 772−775. (b) Saito, S.; Hara, T.; Takahashi, N.; Hirai, M.; Moriwake, T. *Synlett* **1992**, 237−238. (c) Daun, J.; Cheng, C. *Tetrahedron Lett.* **1993**, *34*, 4019−4022. (d) Hosokawa, T.; Sugafugi, T.; Yamanaka, T.; Murahashi, S. *J. Organomet. Chem.* **1994**, *470*, 253−255. (e) Moinet, C.; Fiaud, J. *Tetrahedron Lett.* **1995**, *36*, 2051−2052. (f) Bejeguelal, K.; Joseph, L.; Bolitt, V.; Sinou, D. *J. Carbohydr. Chem.* **2000**, *19*, 221−232.

(31) The cyclizations of oxindoles **17b** and **21b** proceeded more slowly than the previous substrates; after 24 h, significant quantities of starting material remained (ca. 15−20%). Upon heating the mixture for 30 h, the remaining starting material had been reduced to about 3−5%.

(32) As the ^1H NMR spectra for these compounds were complex at room temperature, the ^1H NMR spectrum of the crude reaction mixture was recorded at 100 °C in toluene-d_8.

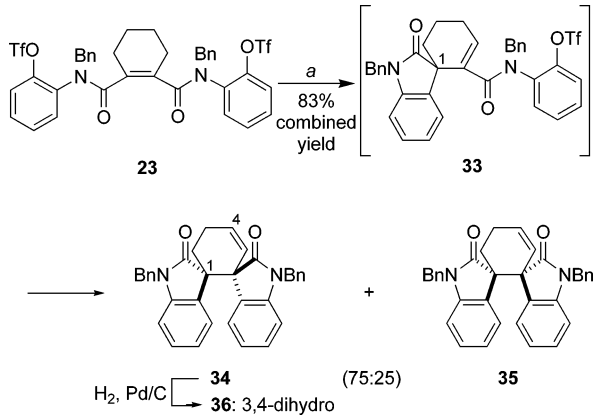
(33) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213−215.

SCHEME 6[a]



[a] Key: (a) 20 mol % $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 24 h; (b) 20 mol % $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 30 h.

SCHEME 7[a]



[a] Key: (a) 20 mol % $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100 °C, 24 h.

in the production of spirooxindole **25** (Scheme 5), with the product of β-siloxy elimination not being observed. The reason for the divergent behavior of the two putative β-siloxy palladium alkyls en route to **28** and **29** is not understood at this time.

The epimeric oxindole precursor **17b** produced pentacyclic dispirooxindoles **31** and **32** in a 91:9 ratio.[31] After chromatographic separation, Heck products **31** and **32** were isolated, respectively, in yields of 61 and 8%; a small amount (7%) of the starting triflate was also recovered. The structure and relative configuration of the major product **31** was determined by single-crystal X-ray diffraction analysis. NMR and mass spectroscopy showed that product **32** lacked a siloxy group at C4. As a result of the small amount of this product isolated, the relative configuration of **32** was not rigorously determined. However, in analogy to the formation of the siloxy cyclohexene **28**, mechanistic reasoning strongly supports the assignment of this minor Heck product as the cis dispirooxindole isomer **32**.

Finally, ditriflate **23**, which lacks the *trans*-diol functionality, cyclized with low stereoselection (Scheme 7). This reaction forms dispirooxindole epimers **34** and **35** (isolated in an 83% combined yield and in a 3:1 ratio). The relative configurations of these products were defined by catalytic hydrogenation of the major isomer **34** to give rise to the C_2-symmetric cyclohexyl dioxindole **36**, whose relative configuration was secured by single-crystal X-ray analysis.

Discussion

The results of Heck cyclizations in the acetonide and disiloxy series reported in Schemes 5 and 6 demonstrate the importance of the initially formed spirooxindole in directing stereoselection of the second Heck cyclization in the cascade double Heck reactions depicted in Scheme 1. In both series, substrates containing a spirooxindole moiety cyclized with significantly higher levels of diastereoselection than substrates lacking this functional group. For example, aryl triflates **17a** and **21a**, which differ in relative configuration of the spirooxindole unit, cyclized to give a single (dr > 20:1) dispirooxindole product. In contrast, cyclization substrate **11** lacking the spirooxindole moiety cyclized with little diastereoselection. In addition, the sense of diastereoselection in forming the second spirooxindole fragment was the same in both the acetonide and disiloxy series. Only the magnitude of diastereoselection varied, being higher in the acetonide series.

The interpretation of these results is straightforward in the acetonide series, because the trans orientation of the acetonide fixes the conformation of the cyclohexene ring. An analysis of the ground-state conformations of these substrates (Figure 1) provides insight into the role of the spirooxindole in regulating stereoselection. In cyclization precursor **17a**, the pseudoaxial arene fragment of the spirooxindole creates significant steric encumbrance about the lower face of the double bond, whereas the oxindole carbonyl oxygen is positioned above the double bond. As the Heck cyclization of spirooxindole **17a** occurs preferentially to the upper face of the double bond, stereoselection could derive from the steric influence of the pseudoaxial

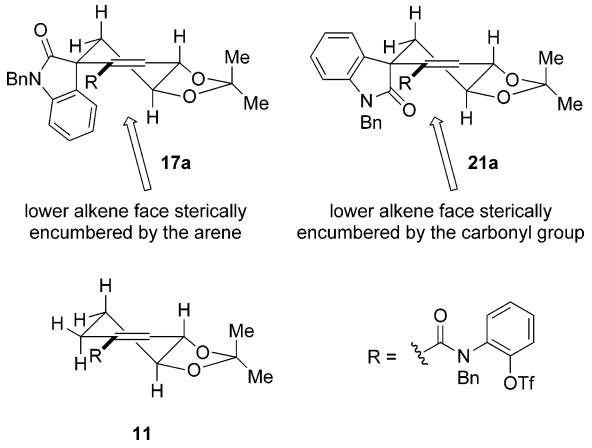


FIGURE 1. Depiction of the conformations of **11**, **17a**, and **21a**. The adjacent axial fragment of the spirooxindole dominates the steric environment of the double bond.

aryl unit, coordination of palladium to the oxindole carbonyl oxygen, or a combination thereof. The observation that spirooxindole epimer **21a** also cyclizes preferentially from the upper face rules out coordination as the major stereodetermining factor in these Heck cyclizations. Thus, the steric influence of the adjacent pseudoaxial substituent is largely regulating facial stereoselection. Consistent with this interpretation is the low facial stereoselectivity seen in the Heck cyclization of substrate **11**, which lacks the spirooxindole substituent.[34]

Stereoselection in the Heck cyclizations of the silyl-protected substrates can be rationalized by similar steric considerations. For these cyclization substrates, two half-chair ground-state conformations must be considered (Figure 2). In the case of Heck precursors **17b** and **21b**, which contain a spirooxindole fragment, the analysis is straightforward as conformation **A**, having the siloxy groups oriented pseudoequatorial, should be much preferred; the alternate conformer **B** suffers from severe 1,3-diaxial interactions. As in the acetonide series, preferential migratory insertion from the face opposite the pseudoaxial aryl fragment of the spirooxindole rationalizes the observed stereoselection in the Heck cyclizations of precursors **17b** and **21b**. The low stereoselectivity observed in the Heck cyclization of substrate **9**, which lacks the spirooxindole group, likely reflects cyclization taking place from both half-chair conformations.[35]

Finally, we consider the modest diastereoselection (3:1) observed in the cyclization of ditriflate **23** (Scheme 7), which lacks oxygen substitution at C4 and C5. Molecular mechanics calculations (MM2) found two low-energy half-chair cyclohexenes for intermediate **33** (Figure 3); these differ in energy by 0.75 kcal/mol, corresponding to an ∼3:1 mixture of conformers at 100 °C. Most likely the similar populations of these conformers contributes to the low stereoselectivity observed in this case. It is tempting to speculate that the small preference observed for the Heck cyclization of **33** to take place

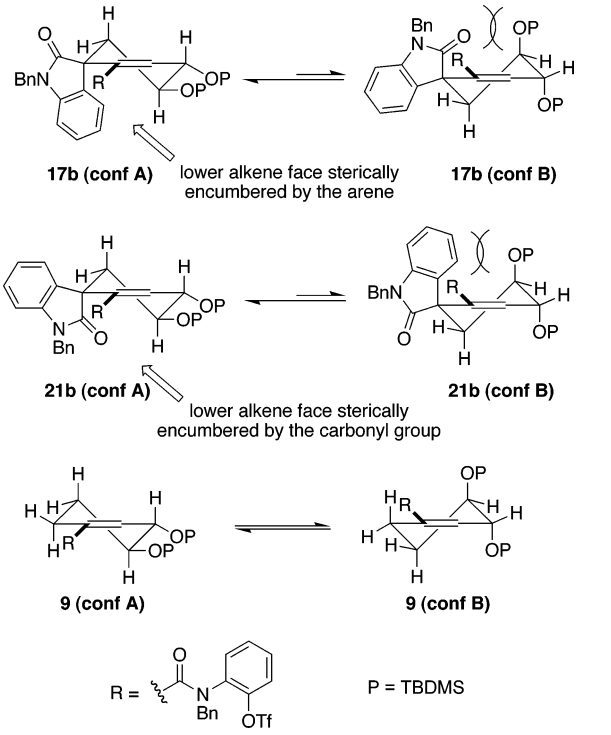


FIGURE 2. Depiction of the two half-chair conformations of **9**, **17b**, and **21b**.

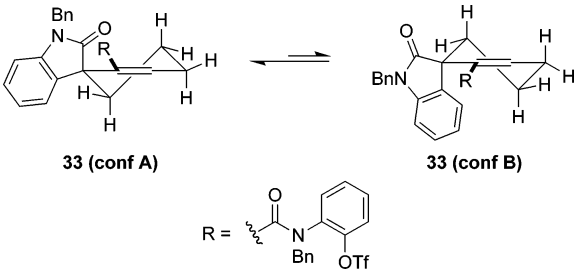


FIGURE 3. Depiction of the two half-chair conformations of **33**; Heck insertion takes place with a 3:1 facial selectivity from the top face.

from the top face of the double bond reflects coordination of the palladium atom to the carbonyl oxygen of the spirooxindole.[36]

Conclusions

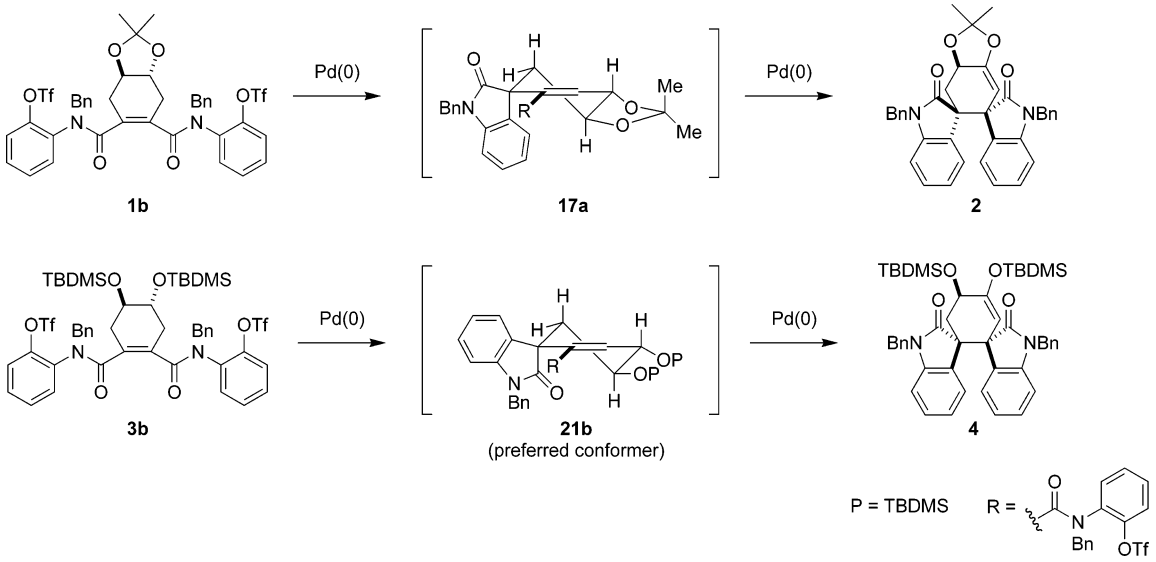
This study investigated the origin of stereoselection in the second ring-closing event in the sequential Heck cyclizations of C_2-symmetric ditriflates **1** and **3**, reactions that assemble complex hexacyclic products containing vicinal quaternary carbon stereocenters. The former substrate, in which the *trans*-C4,C5 diol is masked as an acetonide, exclusively forms

(34) The small level of diastereoselection observed in the cyclization of substrate **11** is consistent with the avoidance of developing eclipsing interactions with the C1 hydrogen atoms, in analogy to the model developed in the previous article.[2]

(35) Because of steric interactions, trans-vicinal siloxy groups destabilize the diequatorial conformation, making it energetically similar to the diaxial conformation. See: Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 15163−15173.

(36) Coordination-controlled Heck reactions have been suggested for various Lewis basic functional groups. For examples, see: (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785−3788. (b) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859−4862. (c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217−8225. (d) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamel, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577−11585. (e) Buezo, N. D.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem.—Eur. J.* **2001**, *7*, 3890−3900. (f) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430−3431. (g) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149−152. (h) Osetreich, M. *Eur. J. Org. Chem.* **2005**, 783−792.

SCHEME 8. Intermediates 17a and 21b, Formed Preferentially in the First Heck Cyclization Step, Undergo the Second Heck Cyclization from the Less-Sterically-Hindered Top Face to Preferentially Form Products 2 and 4



hexacyclic product **2** having trans-related spirooxindole fragments. In contrast, disiloxy congener **3** preferentially forms hexacyclic product **4** in which the newly formed spirooxindoles are cis-related, although stereoselection is lower than in the acetonide series. The presence of the spirooxindole formed in the first step of these sequential cyclizations plays the decisive role in dictating facial stereoselection in the second Heck insertion step. Intermediates **17a** and **21b** are produced preferentially in the first Heck cyclization step.[2] They undergo the second migratory insertion step with high facial selectivity from the less-hindered alkene face (opposite the bulky pseudoaxial fragment of the spirooxindole) in the low-energy conformations depicted in Scheme 8. Substrates analogous to **17a** and **21b** that lack the spirooxindole substituent cyclize with low stereoselection.

Experimental Section[37]

General Procedure for Heck Reactions. In a glovebox under a nitrogen atmosphere, the triflate substrate, $Pd(PPh_3)_2Cl_2$, Et_3N, and DMA were combined in a base-washed glass vial containing a magnetic stir bar. The vial was sealed with a Teflon-lined cap and placed in a 100 °C aluminum heating-block (bored to the diameter of the vial) atop a magnetic stir plate. The reaction was maintained at 100 °C with stirring for 24 h, during which time the initial yellow suspension became a deep red, homogeneous solution.[38] At the end of the indicated time, the reaction was cooled to room temperature, removed from the glovebox, opened to the atmosphere, and diluted with Et_2O. The resultant solution was washed with water twice and once with brine, dried over $MgSO_4$, and concentrated in vacuo. A ^1H NMR analysis of the crude reaction mixture was then used to determine the diastereomeric ratio of the products formed.

Heck Cyclization of Triflate 11. According to the general procedure, triflate **11** (74.1 mg, 145 μmol), $Pd(PPh_3)_2Cl_2$ (20.3 mg, 28.6 μmol), Et_3N (146 mg, 0.20 mL, 1.45 mmol), and DMA (1.4 mL) were heated to give a 63:37 mixture of congeners **24** and **25**. Column chromatography (79:20:1, hexanes/EtOAc/Et_3N) afforded 45.7 mg (87%) of **24** and **25** as a mixture of congeners as a colorless oil. Preparative HPLC (40 mL/min; 89:10:1, hexanes/EtOAc/Et_3N; 300 × 50 mm, 5 μm silica gel column) allowed for the separation of these compounds for characterization.

Data for **24**: IR (film) 2989, 2941, 1706, 1609, 1219, 1127 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.09−7.16 (m, 3H), 7.03 (t, J = 7.1 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.87 (td, J = 7.7, 0.8 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 4.74 (d, J = 15.7 Hz, 1H), 4.52−4.56 (m, 2H), 4.46 (qd, J = 5.5, 1.6 Hz, 1H), 2.20 (td, J = 14.0, 3.3 Hz, 1H), 1.94−1.99 (m, 2H), 1.82−1.90 (m, 1H), 1.49 (dt, J = 13.6, 3.1 Hz, 1H), 1.43 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 180.3, 156.9, 142.3, 137.1, 136.5, 129.3, 128.9, 128.0, 127.8, 124.4, 122.9, 111.9, 109.4, 92.2, 73.5, 50.5, 44.2, 30.9, 27.4, 27.1, 24.9; LRMS (ESI, m/z) 384.11 $(M + Na)^+$; HRMS (EI^+, m/z) calcd for $C_{23}H_{23}NO_3$, 361.1678 $(M)^+$; found, 361.1680.

Data for **25**: IR (film) 2988, 2934, 1702, 1363, 1096 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.07 (d, J = 7.3 Hz, 2H), 6.93−7.01 (m, 3H), 6.84 (td, J = 7.7, 1.3, 1H), 6.77 (td, J = 7.5, 1.1 Hz, 1H), 6.67 (dd, J = 7.4, 0.8 Hz, 1H), 6.37 (d, J = 7.7 Hz, 1H), 4.96 (ddd, J = 16.2, 8.2, 4.2 Hz, 1H), 4.60 (d, J = 15.7 Hz, 1H), 4.54 (d, J = 15.7 Hz, 1H), 3.47 (ddd, J = 12.2, 8.8, 3.8 Hz, 1H), 2.66 (ddd, J = 24.6, 12.0, 4.1 Hz, 1H), 2.18 (ddd, J = 12.5, 4.1, 1.5 Hz, 1H), 1.85−1.94 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 1.46 (td, J = 12.8, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.8, 142.6, 137.0, 134.3, 139.4, 128.7, 128.4, 128.0, 127.8, 109.9, 109.4, 81.2, 75.5, 48.0, 43.6, 37.1, 33.7, 28.0, 27.7, 25.6; LRMS (ESI, m/z) 386.15 $(M + Na)^+$; HRMS (CI^+, NH_3, m/z) calcd for $C_{23}H_{25}NO_3$, 363.1834 $(M)^+$; found, 363.1835.

Heck Cyclization of Triflate 17a. According to the general procedure, triflate **17a** (43.1 mg, 60.0 μmol), $Pd(PPh_3)_2Cl_2$ (8.4 mg, 12.0 μmol), Et_3N (60.7 mg, 77 μL, 600 μmol), and DMA (0.6 mL) were heated to give rise to dioxindole **2** as a single isomer. Column chromatography (90:10, hexanes/EtOAc) afforded 31.1 mg (91%) **2** as a colorless oil. The analytical data for this compound matched that previously reported.[1]

Heck Cyclization of Triflate 21a. According to the general procedure, triflate **21a** (50.7 mg, 70.5 μmol), $Pd(PPh_3)_2Cl_2$ (9.9 mg, 14.1 μmol), Et_3N (71.3 mg, 90 μL, 705 μmol), and DMA (0.7 mL) were heated to give rise to dioxindole **26** as the major product (>95%). Traces (ca. 3−4%) of an additional, unidentified product were observed in the ^1H NMR spectrum of the crude reaction mixture. Repeated attempts failed to isolate this material. Column

(37) (a) General experimental details have been described: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044. (b) CCDC 288976−288978 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(38) On occasion, Pd black was deposited toward the end of the reaction.

chromatography (90:10, hexanes/EtOAc) afforded 35.1 mg (87%) of **26** as a colorless oil: IR (film) 3058, 2991, 2937, 1713, 1609, 1466, 1216 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, $J = 7.4$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 2H), 7.27 (t, $J = 7.3$ Hz, 2H), 7.17−7.23 (m, 2H), 7.04−7.12 (m, 3H), 7.00 (t, $J = 7.5$ Hz, 2H), 6.56 (d, $J = 7.9$ Hz, 1H), 6.51 (t, $J = 8.1$ Hz, 2H), 6.45 (d, $J = 7.6$ Hz, 2H), 5.78 (d, $J = 7.4$ Hz, 1H), 5.53 (d, $J = 9.5$ Hz, 1H), 5.06 (d, $J = 15.6$ Hz, 1H), 4.97 (d, $J = 15.9$ Hz, 1H), 4.92 (d, $J = 15.5$ Hz, 1H), 4.78 (d, $J = 1.9$ Hz, 1H), 4.26 (d, $J = 15.9$ Hz, 1H), 3.55 (dd, $J = 14.3$, 9.6 Hz, 1H), 2.18 (d, $J = 14.4$ Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 176.5, 157.6, 143.4, 142.8, 135.7, 135.1, 132.8, 128.5, 128.8, 128.62, 128.56, 128.5, 127.30, 127.25, 127.0, 126.4, 125.9, 124.2, 122.2, 122.1, 112.1, 109.14, 109.07, 92.4, 70.2, 54.1, 53.3, 44.3, 43.8, 33.9, 27.5, 24.2; LRMS (ESI, *m*/*z*) 569.22 $(M + H)^+$, 591.20 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{37}H_{32}N_2O_4$, 591.2260 $(M + Na)^+$; found, 591.2239.

Heck Cyclization of Triflate 9. According to the general procedure, triflate **9** (211 mg, 301 μmol), $Pd(PPh_3)_2Cl_2$ (42.3 mg, 60.2 μmol), Et_3N (305 mg, 0.42 mL, 3.01 mmol), and DMA (3.0 mL) were heated to give a 57:43 mixture of congeners **27** and **28**. Column chromatography (92.5:7.0:0.5, hexanes/Et_2O/Et_3N) afforded 75.3 mg (45%) of silyl enol ether **27** and 57.8 mg (46%) of alkene **28**, both as colorless oils.

Data for **27**: IR (film) 2954, 2929, 2858, 1713, 1657, 1611, 1250, 1081 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.27 (d, $J = 7.3$ Hz, 1H), 7.14−7.17 (m, 3H), 7.06 (t, $J = 7.3$ Hz, 2H), 6.99 (t, $J = 7.4$ Hz, 1H), 6.88 (t, $J = 7.7$ Hz, 1H), 6.81 (t, $J = 7.4$ Hz, 1H), 6.44 (d, $J = 7.4$ Hz, 1H), 4.74−4.79 (m, 2H), 4.54 (d, $J = 15.6$ Hz, 1H), 4.20 (br s, 1H), 2.90 (br t, $J = 13.3$ Hz, 1H), 2.31 (t, $J = 12.1$ Hz, 1H), 1.70−1.82 (m, 2H), 1.05 (s, 9H), 0.97 (s, 9H), 0.25 (s, 3H), 0.10−0.13 (m, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.1, 156.5, 142.6, 137.0, 135.5, 129.0, 128.4, 127.7, 127.5, 124.0, 122.9, 109.0, 106.1, 68.2, 49.5, 43.5, 29.3, 28.2, 26.22, 26.17, 18.5, 18.4, −3.98, −4.01, −4.04, −4.5; LRMS (ESI, *m*/*z*) 550.4 $(M + H)^+$, 572.4 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{47}NO_3Si_2$, 572.2992 $(M + Na)^+$; found, 572.3004.

Data for **28**: IR (film) 2954, 2929, 2856, 1711, 1611, 1250, 1081 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.14−7.17 (m, 2H), 7.04 (t, $J = 7.3$ Hz, 2H), 6.98 (t, $J = 7.4$ Hz, 1H), 6.88−6.94 (m, 2H), 6.82 (t, $J = 7.5$ Hz, 1H), 6.46 (d, $J = 7.7$ Hz, 1H), 6.04 (d, $J = 9.9$ Hz, 1H), 5.23 (d, $J = 9.9$ Hz, 1H), 4.68 (d, $J = 15.6$ Hz, 1H), 4.56 (d, $J = 15.6$ Hz, 1H), 4.34 (br s, 1H), 2.59−2.70 (m, 1H), 2.10−2.18 (m, 1H), 1.84−1.91 (m, 1H), 1.66 (t, $J = 11.4$ Hz, 1H), 1.01 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.1, 156.5, 142.6, 137.0, 135.5, 129.0, 128.4, 127.7, 127.5, 124.0, 122.9, 109.0, 106.1, 68.2, 49.5, 43.5, 29.3, 28.2, 26.22, 26.17, 18.5, 18.4, −3.98, −4.01, −4.04, −4.5; LRMS (ESI, *m*/*z*) 420.07 $(M + H)^+$, 437.09 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{33}NO_2Si$, 420.2359 $(M + H)^+$; found, 420.2372.

Heck Cyclization of Triflate 21b. In a modification of the general procedure, triflate **21b** (74.0 mg, 81.6 μmol), $Pd(PPh_3)_2Cl_2$ (11.4 mg, 16.3 μmol), Et_3N (82.5 mg, 110 μL, 815 μmol), and DMA (0.8 mL) were heated for 30 h to give a 75:9:16 mixture of compounds **4**, **29**, and **30** along with traces of starting material (ca. 3%). Shorter reaction times resulted in a lower conversion of the starting material. As a result of the uninterpretable complexity at room temperature, the ^1H NMR spectrum of the crude reaction mixture was recorded at 100 °C in toluene-d_8. Column chromatography (88:12−80:20, hexanes/Et_2O) afforded 32.0 mg (52%) of **4** as a colorless foam, 3.7 mg (6%) of **29** as a colorless solid, and 8.5 mg (14%) of **30** as a colorless oil. No starting material was recovered. The analytic data for **4** and **30** matched that previously reported.[2]

Data for **4**: IR (film) 2954, 2929, 2858, 1719, 1652, 1611, 1360, 1250, 1171 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, rt) δ 8.43 (br s, 1H), 7.29 (br s, 2H), 7.05 (br s, 2H), 6.82−6.70 (m, 7H), 6.76 (br s, 1H), 6.15−6.43 (m, 5H), 4.93−5.10 (m, 3H), 4.64−4.80 (m, 2H), 4.26 (br s, 1H), 3.80 (br d, $J = 15.0$ Hz, 1H), 2.01 (br d, $J = 13.0$ Hz, 1H), 1.02 (s, 9H), 0.89 (s, 9H), 0.15−0.25 (m, 9H), −0.14 (br s, 3H); ^{13}C NMR (125 MHz, C_6D_6, rt) δ 177.1, 176.4, 156.5, 144.6, 143.7, 137.2, 136.3, 131.3, 130.6, 130.1, 129.3, 129.2, 129.1, 129.0, 128.7, 127.7, 127.4, 126.8, 125.9, 122.2, 121.8, 109.7, 109.4, 106.4, 67.1, 55.1, 52.0, 45.0, 43.7, 37.2, 26.6, 26.4, 19.1, 18.5, −3.3, −3.4, −3.9, −4.2; LRMS (ESI, *m*/*z*) 757.73 $(M + H)^+$, 779.7 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{46}H_{56}N_2O_4Si_2$, 779.3676 $(M + Na)^+$; found, 779.3684. The ^1H NMR spectrum was also recorded in toluene-d_8 at 100 °C and $CDCl_3$ at room temperature.[28]

Data for **29**: IR (film) 2929, 2856, 1698, 1611, 1362, 1096 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.43 (dd, $J = 7.4$, 0.9 Hz, 2H), 6.98−7.16 (m, 10H), 6.62 (td, $J = 7.7$, 1.3 Hz, 2H), 6.57 (td, $J = 7.6$, 1.1 Hz, 2H), 6.11 (d, $J = 7.1$ Hz, 2H), 5.28−5.34 (m, 2H), 4.86 (d, $J = 15.6$ Hz, 2H), 4.30 (d, $J = 15.6$ Hz, 2H), 3.53−3.62 (m, 2H), 2.05 (dd, $J = 13.9$, 4.0 Hz, 2H), 1.02 (s, 18H), 0.28 (s, 6H), 0.21 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 178.1, 142.9, 136.7, 130.1, 129.3, 128.8, 128.1, 125.0, 123.1, 109.3, 71.4, 53.0, 43.8, 38.9, 26.8, 18.7, −3.1, −4.1; LRMS (ESI, *m*/*z*) 759.73 $(M + H)^+$, 781.71 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{46}H_{58}N_2O_4Si_2$, 781.3833 $(M + Na)^+$; found, 781.3836. The ^1H NMR spectrum was also recorded in toluene-d_8 at 100 °C.[28]

Heck Cyclization of Triflate 17b. In a modification of the general procedure, triflate **17b** (111 mg, 122 μmol), $Pd(PPh_3)_2Cl_2$ (17.1 mg, 24.4 μmol), Et_3N (123 mg, 0.17 mL, 1.22 mmol), and DMA (1.2 mL) were heated for 30 h at 100 °C to give a 91:9 mixture of compounds **31** and **32**, along with traces of remaining starting material (ca. 5%). As a result of the complexity at room temperature, the ^1H NMR spectrum of the crude reaction mixture was recorded at 100 °C in toluene-d_8. Column chromatography (95:5−85:15, hexanes/EtOAc) afforded 59.8 mg (65%) of **31** as a colorless solid, 6.4 mg (8%) of **32** as a colorless solid, and 7.7 mg (7%) of recovered **17b**. Slow diffusion of *n*-hexane into an EtOAc solution of **31** provided crystals suitable for X-ray crystallographic analysis.

Data for **31**: IR (film) 2934, 2860, 1710, 1660, 1640, 1220, 1100 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, rt) δ 7.70−7.75 (m, 1H), 7.47 (d, $J = 6.8$ Hz, 1H), 7.00−7.10 (m, 11H), 6.66−6.80 (m, 3H), 6.61 (td, $J = 6.6$, 1.0 Hz, 1H), 6.13−6.18 (m, 2H), 4.98 (s, 1H), 4.82 (d, $J = 15.8$ Hz, 1H), 4.75 (d, $J = 6.3$ Hz, 1H), 4.69 (d, $J = 15.7$ Hz, 1H), 4.51 (dd, $J = 15.9$, 2.1 Hz, 1H), 3.93 (dd, $J = 14.8$, 6.5 Hz, 1H), 2.06 (d, $J = 14.8$ Hz, 1H), 1.07 (s, 9H), 1.05 (s, 9H), 0.34 (s, 3H), 0.30 (s, 3H), 0.25 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, rt) δ 177.4, 175.3, 156.3, 143.6, 143.5, 136.9, 136.6, 131.5, 130.4, 129.2, 129.2, 129.1, 128.9, 128.7, 128.6, 128.1, 128.03, 127.96, 127.8, 127.0, 125.0, 123.2, 122.5, 109.3, 109.1, 104.5, 66.7, 54.8, 49.9, 44.3, 43.8, 39.3, 26.8, 26.7, 19.2, 18.7, −3.07, −3.11, −3.5, −4.1; LRMS (ESI, *m*/*z*) 757.43 $(M + H)^+$, 779.41 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{46}H_{56}N_2O_4Si_2$, 779.3676 $(M + Na)^+$; found, 779.3669. The ^1H NMR spectrum was also recorded in toluene-d_8 at 100 °C.[28]

Data for **32**: IR (film) 2929, 2856, 1723, 1609, 1488, 1466, 1100 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, rt) δ 7.61 (d, $J = 6.6$ Hz, 1H), 7.29 (d, $J = 7.4$ Hz, 2H), 7.01 (t, $J = 7.2$ Hz, 2H), 6.94 (dd, $J = 10.7$, 7.4 Hz, 2H), 6.87 (t, $J = 7.7$ Hz, 2H), 6.83 (td, $J = 6.8$, 1.5 Hz, 2H), 6.75 (td, $J = 7.8$, 1.2 Hz, 1H), 6.40 (d, $J = 7.7$ Hz, 1H), 6.25−6.35 (m, 4H), 6.19 (dd, $J = 7.2$, 1.4 Hz, 2H), 5.40 (dd, $J = 9.2$, 1.9 Hz, 1H), 5.01−5.06 (m, 1H), 4.97 (d, $J = 16.2$ Hz, 1H), 4.88 (d, $J = 15.8$ Hz, 1H), 4.71 (d, $J = 15.5$ Hz, 1H), 4.25 (dd, $J = 12.6$, 9.6 Hz, 1H), 3.85 (d, $J = 16.2$ Hz, 1H), 2.00 (q, $J = 6.3$ Hz, 1H), 1.03 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, rt) δ 175.8, 174.7, 144.9, 143.7, 137.1, 137.0, 136.0, 131.4, 129.9, 129.4, 129.3, 129.2, 129.1, 128.7, 127.9, 127.8, 127.4, 126.8, 126.4, 126.0, 122.2, 121.7, 110.1, 109.6, 67.5, 56.5, 53.6, 45.2, 43.5, 34.9, 26.5, 18.8, −3.6, −3.7; LRMS (ESI, *m*/*z*) 627.62 $(M + H)^+$, 649.59 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{40}H_{42}N_2O_3Si$, 649.2863 $(M + Na)^+$; found, 649.2852. The ^1H NMR spectrum was also recorded in toluene-d_8 at 100 °C.[28]

Heck Cyclization of Triflate 23. According to the general procedure, triflate **23** (242 mg, 304 μmol), $Pd(PPh_3)_2Cl_2$ (42.6 mg,

60.8 μmol), Et_3N (307 mg, 0.42 mL, 3.04 mmol), and DMA (3.0 mL) were heated to give a 75:25 mixture of epimers **34** and **35**. Column chromatography (90:10−85:15, hexanes/EtOAc) afforded 96.6 mg (64%) of **34** as a colorless solid and 28.7 mg (19%) of **35** as a colorless foam.

Data for **34**: IR (film) 3029, 2916, 1704, 1609, 1488, 1466, 1360, 1173 cm^{-1}; ^1H NMR (500 MHz, toluene-d_8, rt) δ 7.46 (d, J = 7.4 Hz, 2H), 6.93−7.03 (m, 10H), 6.67−6.72 (m, 2H), 6.58−6.64 (m, 2H), 6.22 (ddd, J = 9.9, 4.8, 2.5 Hz, 1H), 6.14 (d, J = 7.7 Hz, 1H), 5.34 (dt, J = 9.9, 1.9 Hz, 1H), 4.60 (d, J = 15.7 Hz, 2H), 4.50−4.55 (m, 2H), 3.00−3.11 (m, 1H), 2.24 (dt, J = 18.4, 4.9 Hz, 1H), 1.53 (dd, J = 13.9, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, toluene-d_8, rt) δ 176.4, 176.0, 143.4, 143.0, 136.5, 136.3, 132.2, 131.0, 130.7, 129.2, 128.8, 128.7, 128.5, 128.23, 128.16, 127.7, 127.6, 127.5, 127.4, 126.2, 125.1, 123.9, 108.8, 108.6, 53.5, 50.4, 44.0, 43.4, 26.8, 22.3; LRMS (ESI, m/z) 497.25 $(M + H)^+$, 519.23 $(M + Na)^+$; HRMS (ESI, m/z) calcd for $C_{34}H_{28}N_2O_2$, 497.2229 $(M + Na)^+$; found, 497.2231.

Data for **35**: IR (film) 3029, 2912, 1715, 1609, 1488, 1466, 1349, 1177 cm^{-1}; ^1H NMR (500 MHz, toluene-d_8, rt) δ 7.53 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 7.4 Hz, 2H), 7.00−7.04 (m, 2H), 6.91−6.96 (m, 2H), 6.82−6.90 (m, 4H), 6.77 (t, J = 7.7 Hz, 1H), 6.22−6.40 (m, 5H), 6.11 (d, J = 7.4 Hz, 1H), 6.02 (dt, J = 9.7, 3.4 Hz, 1H), 5.45 (d, J = 9.9 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 4.84 (d, J = 15.8 Hz, 1H), 4.74 (d, J = 15.8 Hz, 1H), 3.85−3.96 (m, 2H), 3.39−2.49 (m, 1H), 2.20−2.32 (m, 1H), 1.37 (dd, J = 13.3, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, toluene-d_8, rt) δ 176.9, 175.3, 144.6, 143.5, 137.5, 137.3, 136.9, 136.1, 132.5, 131.6, 130.2, 129.2, 128.6, 128.3, 127.3, 127.1, 126.6, 126.2, 125.5, 125.3, 122.0, 121.4, 109.33, 109.26, 53.1, 52.6, 44.8, 43.2, 25.1, 22.7; LRMS (ESI, m/z) 497.26 $(M + H)^+$, 519.24 $(M + Na)^+$; HRMS (ESI, m/z) calcd for $C_{34}H_{28}N_2O_2$, 497.2229 $(M + Na)^+$; found, 497.2245.

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Supporting Information Available: Complete experimental details for the preparation of the substrates and the chemical correlation of the products, copies of ^1H and ^{13}C NMR spectra of all new compounds, and NOE data used in the assignment of the configurations of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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