JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

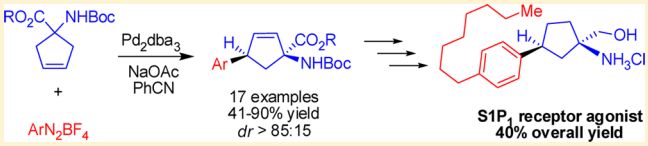
Stereoselective Arylation of Substituted Cyclopentenes by Substrate-Directable Heck–Matsuda Reactions: A Concise Total Synthesis of the Sphingosine 1-Phosphate Receptor ($S1P_1$) Agonist VPC01091

Caio C. Oliveira, Emerson A. F. dos Santos, Julia H. Bormio Nunes, and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP, 13083-970, Campinas, São Paulo, Brazil

Supporting Information

ABSTRACT: We describe herein an efficient and diastereoselective substrate-directable Heck–Matsuda reaction with nonactivated five-membered olefins. The carbamate acts as the main directing group in the arylation process allowing the synthesis of several functionalized aryl cyclopentenes in good to excellent diastereoselectivities (>85:15) and in isolated yields ranging from 41 to 90%. No double bond isomerizations were observed in these Heck reactions, and the newly created benzylic centers were preserved in all cases examined. The substrate directable Heck arylation approach was successfully applied in a straightforward total synthesis of the sphingosine 1-phosphate receptor-subtype 1 ($S1P_1$) agonist VPC01091 by a concise and practical route involving 5 steps in 40% overall yield.



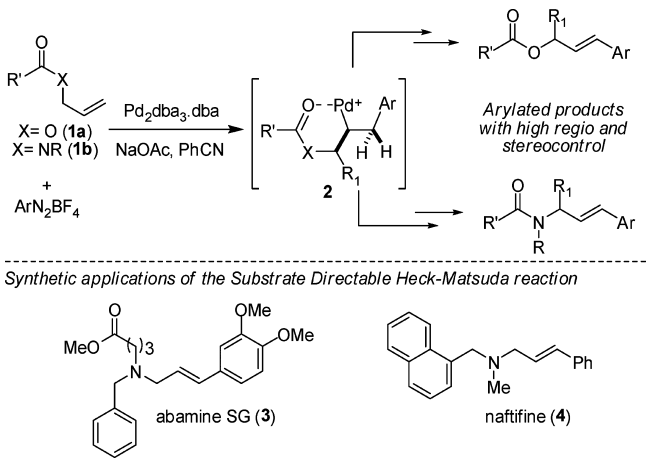
INTRODUCTION

The Heck reaction is nowadays a popular and powerful synthetic method for constructing C–C bonds.[1] The Heck–Matsuda version of the Heck reaction derives from the use of arenediazonium salts (mainly the thermostable tetrafluoroborates) as the arylating agents instead of the conventional aryl halides or aryl triflates.[2] The higher reactivity of arenediazonium salts is related to the liability of the $Csp^2–N_2^+$ bond, making them the most active substrates for oxidative addition to palladium. The resulting cationic arylpalladium intermediates are very reactive, thus allowing many of the arylations to be performed within shorter reaction times and milder conditions when compared to the conventional Heck reactions. Furthermore, the Heck–Matsuda reactions are typically carried out under phosphine-free and aerobic conditions in a very practical and economical way.

We have demonstrated in previous studies that the reactivity of the cationic palladium species generated after oxidative addition can be modulated and controlled by substrates possessing chelating groups such as allylic esters **1a** and amides **1b**.[3,4] This process was denominated substrate-directable Heck–Matsuda and was successfully applied as a key strategy in the synthesis of bioactive compounds, such as the vegetal hormone abamine SG (**3**) and the antifungal drug naftifine (**4**). The new C–C bond was formed with high levels of stereocontrol, and the formation of the (*E*)-styrene products was attributed to the anchimeric assistance of the carbonyl moiety present in the substrates (**2**) (Scheme 1).[5]

Because of the remarkable selectivity observed in the aforementioned studies, we decided to choose a more challenging substrate to evaluate the scope of these substrate-directed Heck–Matsuda reactions. The use of olefins featuring two or more potentially chelating functional groups poses interesting questions concerning the origins of the stereocontrol and might provide insights into the nature of the arylating palladium species. To investigate the viability of this approach, we chose as initial prototypes the readily available, nonactivated olefins **6a,b** possessing strategically located ester and carbamate functional groups, which could potentially direct the insertion of the aryl palladium intermediates.[6] If this is successful, the Heck products derived from these studies were envisaged as potential intermediate for the total synthesis of bioactive compounds, as explained below.

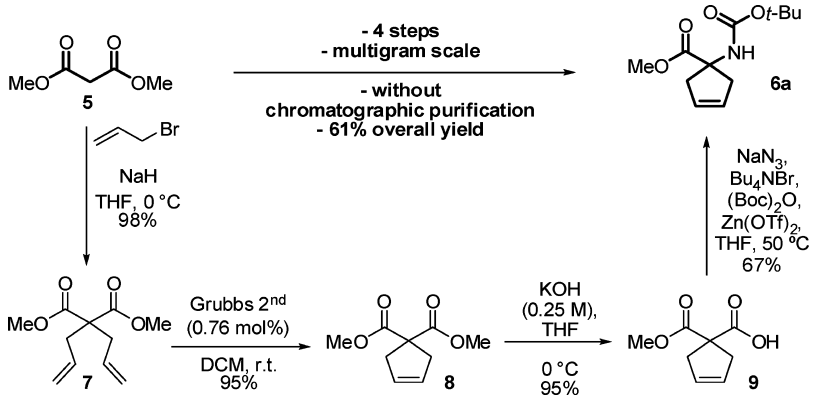
Scheme 1. Heck–Matsuda Reaction of Allylic Esters 1a and Amides 1b



Received: July 23, 2012
Published: August 27, 2012

   dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182–8190

Scheme 2. Multigram Synthesis of the Olefin 6a



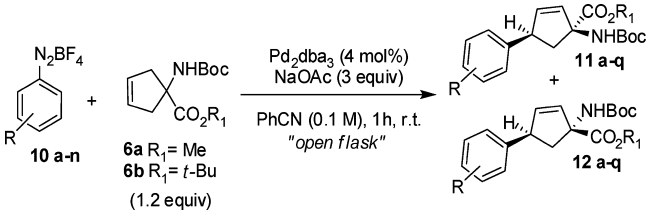
RESULTS AND DISCUSSION

Our approach for the multigram synthesis of the olefin **6a** began with the diallylation of dimethyl malonate (**5**) with allyl bromide, followed by a ring-closing metathesis[7] and a partial hydrolysis of the malonate moiety to provide the monoester **9**.[8] The last step consisted of the Curtius rearrangement, and it was carried out according to the *one-pot* methodology developed by Lebel.[9] All these reactions were very clean, and the final product was obtained in pure form at the end of the process without purification by column chromatography (Scheme 2).

We began our investigation on the Heck arylation using conditions similar to those previously reported for the arylation of allylic amides **1b** with arenediazonium salts **10**, that is, a slight excess of olefin (1.2 equiv), NaOAc (3 equiv) and $Pd_2(dba)_3$ (4 mol %) in benzonitrile as solvent.[4] Reactions were carried out under open vessel conditions at room temperature for 1 h to provide the corresponding aryl cyclopentene in good to excellent yields as depicted in Table 1. The scope of the Heck arylations proved to be broad with a diverse array of arenediazonium salts providing the corresponding aryl cyclopentene products (17 examples, Table 1) in good to excellent yields in most cases. Remarkably, in all instances the Heck arylation gave the *syn* adduct with respect to the *t*-butoxy carbamate group as the main stereoisomer. Aiming at future synthetic applications, the *p*-alkyl-substituted Heck products were obtained with good levels of stereochemical control (entries 1−8). Complete chemoselectivity was achieved with 4-iodobenzenediazonium tetrafluoroborate (**10i**), making the products **11i** and **11j** valuable substrates for other cross-coupling reactions (entries 9 and 10). Several regioisomeric dimethoxy aryldiazonium salts produced the Heck adducts in good yields (entries 11 to 16). The electron-deficient *p*-cyano benzenediazonium tetrafluoroborate also provided the corresponding Heck adduct in good yield and stereoselectivity (entry 17). A decrease in yield was observed when *t*-butyl esters were evaluated (compare entries 9−10 and 14−15). An explanation for these results is the congestion created by two bulky geminal groups, thus affecting the complexation of the arylpalladium to the carbamate carbonyl group and the double bond as illustrated in Scheme 3.

A plausible catalytic cycle for this reaction starts with the oxidative addition of the Pd(0) (**A**) to the arenediazonium salt **10** to produce the cationic arylpalladium **B** (Scheme 3). We hypothesize that this intermediate is chelated by the olefin preferably by the same face of the carbamate group as depicted in **C**. We also reasoned that this preferential chelation occurs

Table 1. Scope of the Heck−Matsuda Reaction with Olefins 6a,b



entry	R	R_1	11a−q/12a−q	yield (%)[a]
1	*p*-methyl (**10a**)	Me	85/15	90
2	*p*-ethyl (**10b**)	Me	87/13	56
3	*p*-propyl (**10c**)	Me	>95/5	90
4	*p*-butyl (**10d**)	Me	90/10	71
5	*p*-pentyl (**10e**)	Me	85/15	80
6	*p*-hexyl (**10f**)	Me	86/14	85
7	*p*-heptyl (**10g**)	Me	87/13	78
8	*p*-octyl (**10h**)	Me	88/12	90
9	*p*-I (**10i**)	Me	86/14	58
10	*p*-I (**10i**)	*t*-Bu	94/6	41
11	2,4-OMe (**10j**)	Me	>95/5	70
12	2,5-OMe (**10j**)	Me	89/11	65
13	2,5-OMe (**10k**)	*t*-Bu	86/14	40
14	3,4-OMe (**10l**)	Me	87/13	90
15	3,4-OMe (**10l**)	*t*-Bu	85/15	64
16	*p*-NHCbz (**10m**)	Me	85/15	70
17	*p*-CN (**10n**)	Me	88/12	68

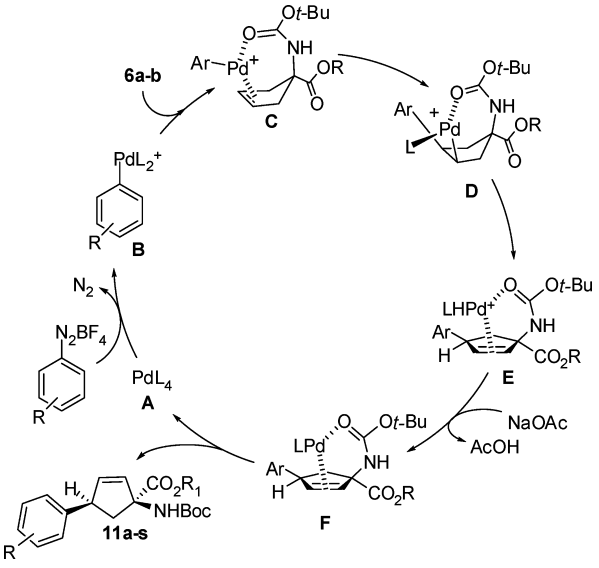
[a]Isolated yields. Average of at least two experiments.

because the carbamate has an electron-richer carbonyl moiety and the intermediate formed with this configuration is less strained than the alternative chelation involving the interaction of the arylpalladium species **B** with the double bond and the ester carbonyl group. Next, migratory insertion places the aryl group *syn* to the carbamate group as in (**D**). Finally, *β*-elimination leads to the formation of product **11** still complexed to the palladium hydride, as in (**E**). Hydrogen abstraction by NaOAc generates intermediate **F**, which undergoes decomplexation to the Heck product and Pd(0) for another catalytic cycle (Scheme 3).

It is worth mentioning that in all reactions performed, we observed that the starting olefin **6a** (used in slightly excess of 1.2 equiv) isomerizes partially in the reaction medium. We rationalized this intriguing observation as a potential indication that the starting olefin may be acting as a scavenger for the

dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182−8190

Scheme 3. Proposed Catalytic Cycle



palladium hydride in intermediate **E** forming a new palladium complex, which under β-elimination produces the isomerized starting material (Scheme 4). On the other hand, the Heck adduct **11** does not seem to have the same capability, thus restricting the formation of undesirable isomers. This isomeric olefin **6c** proved inactive to the Heck–Matsuda arylation.

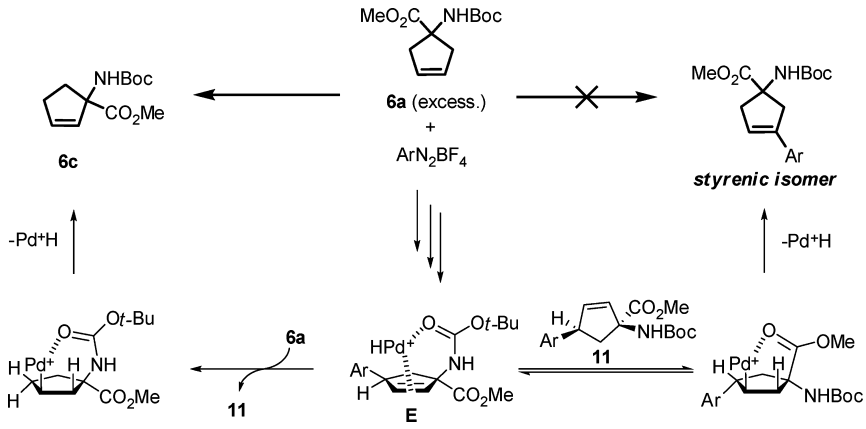
In spite of the remarkable advances in the field of Heck–Matsuda reactions in recent years,[10] a common problem with nonactivated carbocyclic olefins is the frequent attainment of inseparable mixtures of isomers[11a–g] or the exclusive formation of the conjugated Heck products as illustrated in recent reports.[12a–c] In the present case, we believe that steric congestion around the olefin in the Heck product **11** prevents such isomerization to a styrene product as indicated in Scheme 4.

Assignment of the Relative Stereochemistry for the Heck Adducts. The critical assignments for hydrogen H1 and H2 were based on literature precedents for similar systems.[13] These precedents indicated the hydrogen syn to the ester as the more deshielded one. Therefore, hydrogen H_1, *syn* to the carbamate group, is observed in the ^{1}H NMR spectrum at ~1.8 ppm as a double doublet with coupling constants of 7.5 and 13.5 Hz, while H_2 (*syn* to the ester group) appears at ~3.3 ppm as another double doublet with coupling constants of 8.5 and 13.5 Hz (see Figure 1). The benzylic proton (H_3) is observed at ~4.2 ppm as a triplet with J = 7.5 Hz. In order to confirm the relative position of aromatic ring, we performed NOE (nuclear Overhauser effect) experiments with the Heck adduct **11n**. Irradiation of the benzylic hydrogen (H_3) induced a NOE increment of 0.8% in H_1 and 3.5% in H_2, indicating the greater proximity between H_2 and H_3. Further evidence came from irradiation of H_1, leading to a NOE increment of the *ortho* aromatic hydrogens of 1.4%. These stereochemical assignments were confirmed by the conversion of the Heck adducts **11h** and **11i** into the S1P$_1$ receptor agonist VPC01091 **16**, as described below.

Figure 1. Stereochemical assignment and NOE increments for the Heck product **11n**.

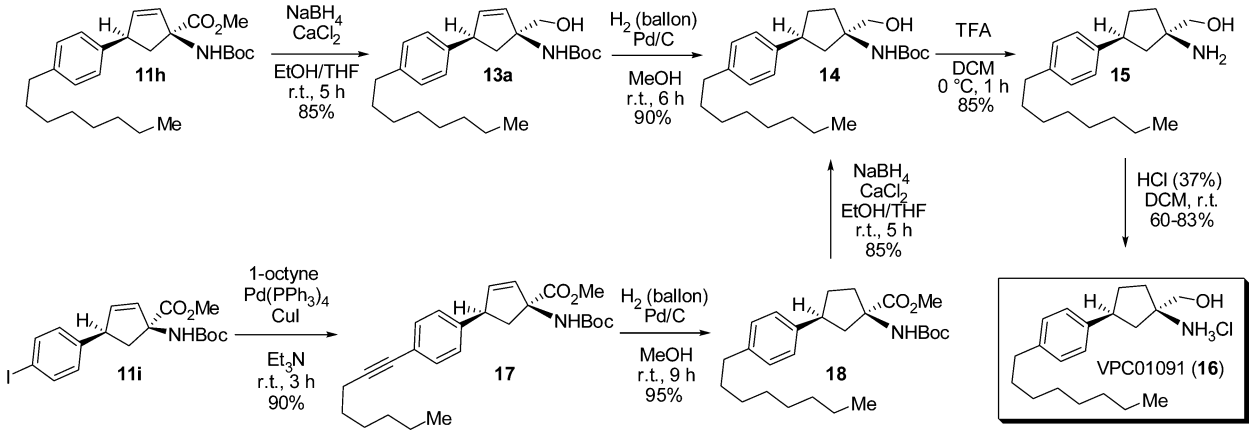
Synthetic Applications. To further demonstrate the scope and the synthetic utility of this novel Heck–Matsuda arylating method, we performed a short stereoselective total synthesis of the compound VPC01091 (**16**), an orally active and selective agonist for the sphingosine-1-phosphate receptor-subtype 1 (S1P$_1$) (Scheme 5).[14a–d] These agonists constitute an important class of drugs for the treatment of multiple sclerosis without significant side effects on the cardiovascular system.[14–16] The *anti*-hydroxymethyl aryl alcohol **14** was the key intermediate in our total synthesis, and it was successfully synthesized by two different routes. In the first one, the ester moiety in the Heck adduct **11h** was reduced with NaBH$_4$/CaCl$_2$ in EtOH/THF[17a,b] to provide the alcohol **13a** in good yield (85%).[18] Hydrogenation of the olefin in **13a** catalyzed by Pd/C gave the desired cyclopentane **14** in 90% yield.[18] The second approach to alcohol **14** was performed using the Heck adduct **11i** as the starting material. The importance of maintaining an aryl iodide moiety for future functionalization was demonstrated during insertion of the alkyl side chain by a Sonogashira cross-coupling reaction. The coupling of **11i** with 1-octyne (2 equiv), using Pd(PPh$_3$)$_4$ (1 mol %) and CuI (2 mol

Scheme 4. Proposed Pathway for the Isomerization of 6a

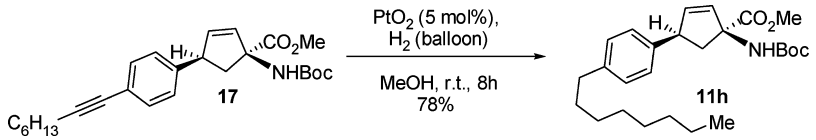


dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182–8190

Scheme 5. Synthesis of VPC01091



Scheme 6. Chemoselective Hydrogenation of the Enyne 17



%) as catalysts and triethylamine as solvent provided the disubstituted alkyne **17** in 90% yield after 3 h at room temperature.[19] Next, the cyclopentane **14** was generated by simultaneous hydrogenation of the double and triple bonds catalyzed by Pd/C (95% yield), followed by reduction of the ester group with $NaBH_4/CaCl_2$ in EtOH/THF[17a,b] (85% yield). Finally, the synthesis of the VPC01091 was completed by removal of Boc protecting group of alcohol **14** with trifluoroacetic acid in dichloromethane at 0 °C in good yield (85%), followed by formation of the corresponding hydrochloride by addition of concentrated HCl, according to the literature procedures (Scheme 5).[14b,20]

During our experiments to promote the hydrogenation of the Sonogashira adduct **17**, we had the chance to test several catalysts for the best performance and selectivity. We observed that the Wilkinson's catalyst was completely ineffective, and only the starting material was recovered in this case. On the other hand, the cationic iridium catalyst (Crabtree) was very reactive promoting the reduction of the double and the triple bonds.[21] The heterogeneous catalysts Pd/C and PtO_2 demonstrated interesting selectivity; after 3 h only the reduction of the alkyne moiety was observed (conversion of **17** into **11h**). Extending the reduction time with Pd/C, hydrogenation of the endocyclic double bond is also observed (conversion of **17** into **14**). The catalyst showing the best chemoselectivity for the hydrogenation of the triple bond of enyne **17** was PtO_2 (Scheme 6). When monitoring the reaction by ^1H NMR, we observed only the reduction of the triple bond after 8 h and the almost exclusive formation of compound **11h** in the reaction mixture. After optimization, reduction of the enyne **17** into the cyclopentene **11h** could be performed in 78% yield. The main objective of these studies was to develop a reliable method for the introduction of alkyl chains of any length by the Sonogashira coupling without affecting the double bond originated from the Heck–Matsuda reaction. For practical and economical reasons, Pd/C was chosen for the synthesis of compound **18** from **17** in Scheme 5.

■ CONCLUSIONS

In summary, we developed an effective and diastereoselective method for the construction of several aryl cyclopentenes using an efficient substrate-directable Heck–Matsuda reaction. The scope of this method was shown to be very broad, allowing the synthesis of several functionalized aryl cyclopentenes under "open flask" conditions, at room temperature, in a practical manner. Moreover, the significant increase in structural complexity afforded by this reaction permitted the stereoselective total synthesis of the $S1P_1$ agonist VCP01091 (**16**). The synthesis was accomplished with arenediazonium salts bearing the adequate C_8-alkyl chain or by its introduction in a later stage through a Sonogashira cross-coupling reaction. The synthesis of the sphingosine 1-phosphate receptor-subtype 1 (S1P1) agonist VPC01091 was accomplished by a concise and practical route involving only 5 steps in 40% overall yield.

■ EXPERIMENTAL SECTION

General Methods. Hydrogen nuclear magnetic resonance spectra (^1H NMR) were obtained at 250, 400, 500, and 600 MHz. Spectra were recorded in $CDCl_3$, DMSO-d_6, CD_3OD solutions. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 62.5 MHz, 100 MHz, 125 MHz and 150 MHz. Spectra were recorded in $CDCl_3$, CD_3OD, acetone-d_6 and DMSO-d_6 solutions. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), dd (double doublet), dt (double triplet), td (triple of doublet) and m (multiplet). ESI-HRMS spectra were recorded on a Q-TOF (ESI-QTOF) equipment. Column chromatography was performed using silica gel (230–400 mesh) following the methods described by Still.[22] Thin layer chromatography (TLC) was performed using silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with phosphomolybdic acid, followed by heating. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe techniques. Olefin **6b** is a commercially available compound.

dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182–8190

Methyl 1-(*tert*-butoxycarbonylamino)cyclopent-3-enecarboxylate 6a. *Diallylation of Dimethyl Malonate.* NaH (60% in mineral oil, 9.12 g, 228 mmol) and dry THF (100 mL) were placed in a 500 mL round-bottom flask equipped with a magnetic stir bar. After cooling to 0 °C, a solution of dimethyl-malonate (10.00 g, 76 mmol) in 50 mL of dry THF was slowly added to the NaH suspension. The reaction was stirred at room temperature for 0.5 h, after which allyl bromide (27.58 g; 19.73 mL; 228 mmol) was added at once. The mixture was then warmed to room temperature (~25 °C) and stirred for 3 h. Next, a saturated solution of NH_4Cl was carefully added until complete dissolution of the suspended solid. The aqueous phase was separated and washed with Et_2O (3 × 100 mL). The organic layers were combined, washed with brine (3 × 100 mL), dried over Na_2SO_4, and the solvent removed under reduced pressure to provide an oily residue. This crude product (~20 g) was used in the next step without purification. [This material can be purified by column chromatography, using hexanes:EtOAc (4:1) as eluent, to provide the diallyldimethylmalonate (**7**) in 98% yield (15.7 g; 75 mmol)].

Ring Closing Metathesis. To a solution of the crude diene obtained previously in 700 mL of dichloromethane was added the Grubbs catalyst (second generation; 0.482 g; 0.577 mol; 0.76 mol %). The brown colored mixture was stirred under room temperature for 7 h. Next, the solvent was evaporated to half the initial volume and filtered through a plug of silica gel. The solution was evaporated to afford ~15 g of a pale brown solid residue. This crude material was used in the next step without purification. This compound can be purified by column chromatography, using hexanes:EtOAc (9:1) as eluent, to provide the diester cyclopentene **8** in 95% yield (12.12 g; 71 mmol).

*Partial Hydrolysis of the Diester Cyclopentene **8**.* A 2 L round-bottom flask containing an egg-shaped (5 cm) magnetic stir bar was charged with the crude dimethyl 3-cyclopentene-1,1-dicarboxylate (**8**) obtained previously and dissolved in 120 mL of THF. The resulting mixture was then cooled to 0 °C, followed by addition of 1 L of a cold solution of KOH (0.25 mol/L). The reaction mixture was vigorously stirred at 0 °C for 1 h. Next, the reaction medium was transferred to a 2 L separatory funnel and washed with EtOAc (3 × 400 mL) to remove the residual mineral oil from the first reaction (allylation of malonate). The separated aqueous phase was acidified to pH = 1 by addition of a solution of HCl (1 mol/L) followed by extraction with EtOAc (3 × 400 mL). These organic layers were combined and dried over Na_2SO_4, and the solvent removed under reduced pressure to afford 11.48 g (89% yield, 68 mmol, over 3 steps) of the carboxylic acid **9** as a white solid, homogeneous by ^1H NMR analysis.

One-Pot Curtius Rearrangement. To a suspension of the carboxylic acid **9** (2.55 g; 15.0 mmol), sodium azide (3.41 g, 52.5 mmol), tetrabutylammonium bromide (0.72 g, 2.25 mmol), and $Zn(OTf)_2$ (0.360 g; 1 mmol; 6.6 mol %) in dry THF (150 mL) at 40 °C was added di-*tert*-$(Boc)_2O$ (4.37 g; 19.12 mmol; 4.6 mL). The resulting mixture was then vigorously stirred at 50 °C for 48 h under nitrogen atmosphere. Next, the reaction mixture was added to a 10% solution of $NaNO_2$ (300 mL), diluted with ethyl acetate (300 mL), and stirred at room temperature for 20 min. The organic and aqueous phase was separated, and the aqueous phase extracted with more EtOAc (3 × 250 mL). The organic phases were combined and washed twice with saturated NH_4Cl (2 × 300 mL), followed by washings with saturated $NaHCO_3$ (2 × 300 mL) and brine (2 × 300 mL). The organic phase was then dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to provide a light brown solid. This product can be purified by column chromatography, using hexanes:EtOAc (4:1) as eluent, or recrystallized with hexanes/EtOAc to provide the carbamate **6a** as a white solid in 67% yield (2.43 g; 10 mmol). Spectroscopic data were in accordance with the literature:[23] ^1H NMR $CDCl_3$, 250 MHz, δ (ppm) 5.65 (s, 2H), 5.18 (bs, 1H), 3.75 (s, 3H), 3.06 (d, J = 17.5, 2H), 2.62 (d, J = 17.5, 2H), 1.43 (s, 9H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 174.7, 154.9, 127.61, 79.8, 64.2, 52.5, 44.8, 28.2.

Synthesis of the Arenediazonium Tetrafluoroborates. *General Procedure for **10c–h**.* To a 50 mL beaker were added 6 mmol of the aniline and 6 mL of HCl (3 mol/L). The resulting suspension was cooled to 0 °C followed by slow addition of an aqueous solution of $NaNO_2$ (0.93 g in 1 mL) under vigorous stirring for 15 min. Next, the reaction mixture was transferred to a separatory funnel and washed twice with cold Et_2O (2 × 10 mL). To the aqueous phase remaining in the separatory funnel was then added 3.5 mL of 47% HBF_4. The resulting solution was extracted twice with 15 mL of dichloromethane. The dichloromethane phases were combined, washed with 10 mL of water, dried over anhydrous Na_2SO_4 and evaporated in vacuo to provide the arenediazonium salts as low melting point solids or viscous oils at room temperature.

All the other arenediazonium salts were prepared according to the literature[24] and purified by recrystallization from acetone with cold diethyl ether at 0 °C and stored at −20 °C. Note: The analytical samples for the NMR analysis should be prepared immediately before the analyses because of the decomposition of these salts in acetone.

4-Methyl-benzenediazonium tetrafluoroborate-10a. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.72 (d, J = 7.5, 2H), 7.89 (d, J = 7.5, 2H), 2.68 (s, 3H); ν_{max} (ArN≡N) 2279. Salt obtained as a white solid, mp 109−110 °C.

4-Ethyl-benzenediazonium tetrafluoroborate-10b. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.73 (d, J = 7.5, 2H), 7.93 (d, J = 7.5, 2H), 2.99 (q, J = 7.5, 2H), 1.32 (t, J = 7.5, 3H); ν_{max} (ArN≡N) 2280. Salt obtained as a white solid, mp 110−111 °C.

4-Propyl-benzenediazonium tetrafluoroborate-10c. 0.74 g (53%): ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.73 (d, J = 7.5, 2H), 7.92 (d, J = 7.5, 2H), 2.93 (t, J = 7.5, 2H), 1.76 (sx, J = 7.5, 2H), 0.96 (t, J = 7.5, 3H); ν_{max} (ArN≡N) 2279. Salt obtained as a pale yellow solid, mp 63−64 °C.

4-Butyl-benzenediazonium tetrafluoroborate-10d. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.70 (d, J = 10, 2H), 7.90 (d, J = 10, 2H), 2.94 (t, J = 7.5, 2H), 1.70 (qn, J = 7.5, 2H), 1.40 (sx, J = 7.5, 2H), 0.93 (t, J = 7.5, 3H); ν_{max} (ArN≡N) 2275. Salt obtained as light brown oil.

4-Pentyl-benzenediazonium tetrafluoroborate-10e. 1.24 g (79%): ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.72 (d, J = 9, 2H), 7.93 (d, J = 9, 2H), 2.94 (t, J = 7.6, 2H), 1.75 (qn, J = 7.5, 2H), 1.35 (m, 4H), 0.86 (t, J = 6.8, 3H); ν_{max} (ArN≡N) 2279. Salt obtained as a pale yellow oil.

4-Hexyl-benzenediazonium tetrafluoroborate-10f. 1.29 g (78%): ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.73 (d, J = 8.8, 2H), 7.94 (d, J = 8.8, 2H), 2.96 (t, J = 7.8, 2H), 1.74 (qn, J = 7.5, 2H), 1.35 (m, 6H), 0.86 (t, J = 7, 3H); ν_{max} (ArN≡N) 2279. Salt obtained as a light green oil.

4-Heptyl-benzenediazonium tetrafluoroborate-10g. 1.25 g (72%): ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.73 (d, J = 8.8, 2H), 7.93 (d, J = 8.8, 2H), 2.96 (t, J = 7.8, 2H), 1.74 (qn, J = 7.5, 2H), 1.35 (m, 8H), 0.86 (t, J = 7, 3H); ν_{max} (ArN≡N) 2280. Salt obtained as a pale yellow oil.

4-Octyl-benzenediazonium tetrafluoroborate-10h. 1.55 g (85%): ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.78 (d, J = 8.8, 2H), 7.94 (d, J = 8.8, 2H), 2.97 (t, J = 7.8, 2H), 1.74 (qn, J = 7.5, 2H), 1.35 (m, 10H), 0.86 (t, J = 6.8, 3H); ν_{max} (ArN≡N) 2280. Salt obtained as a light brown oil.

4-Iodo-benzenediazonium tetrafluoroborate-10i. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.52 (s, 4H); ν_{max} (ArN≡N) 2284. Salt obtained as an off white solid, mp 115−116 °C.

2,4-Dimethoxy-bezenediazonium tetrafluoroborate-10j. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.46 (d, J = 10, 1H), 7.18 (d, J = 2.5, 1H), 7.03 (dd, J = 2.5 and 10, 1H), 4.31 (s, 3H), 4.17 (s, 3H); ν_{max} (ArN≡N) 2214. Salt obtained as a purple solid, mp 110−111 °C.

2,5-Dimethoxy-bezenediazonium tetrafluoroborate-10k. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.06 (d, J = 2.5, 1H), 7.89 (dd, J = 2.5 and 10, 1H), 7.70 (d, J = 10, 1H), 4.28 (s, 3H), 3.91 (s, 3H); ν_{max} (ArN≡N) 2252. Salt obtained as a dark red solid, mp 106−107 °C.

3,4-Dimethoxy-bezenediazonium tetrafluoroborate-10l. ^1H NMR acetone-d_6, 250 MHz, δ (ppm) 8.56 (dd, J = 2.5 and 10, 1H), 8.23 (d, J = 2.5, 1H), 7.56 (d, J = 10, 1H), 4.17 (s, 3H), 3.99 (s, 3H); ν_{max} (ArN≡N) 2249. Salt obtained as a purple solid, mp 104−105 °C.

4-(Benzyloxycarbonylamino)phenyldiazonium tetrafluoroborate-10m. ^1H NMR CD_3CN, 250 MHz, δ (ppm) 9.03 (bs, 1H),

dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182−8190

8.34 (d, J = 9.4, 2H), 7.94 (d, J = 9.4, 2H), 7.43 (m, 1H), 5.27 (s, 2H). Salt obtained as a yellow solid, mp 138−139 °C.

4-Cyano-bezenediazonium tetrafluoroborate-10n. ^{1}H NMR acetone-d_6, 250 MHz, δ (ppm) 9.07 (d, J = 10, 2H), 8.51 (d, J = 10, 2H). (ArN≡N) 2297. Salt obtained as a yellow solid, mp 119−120 °C.

General Procedure for the Heck−Matsuda Reaction. To a round-bottomed flask (or a test tube) were added $Pd_2(dba)_3$ (4 mol %, 9.2 mg), sodium acetate (3 equiv, 0.062 g) and benzonitrile (2.5 mL). To the resulting suspension was then added the olefin **6a,b** (1.2 equiv, 0.3 mmol) followed by addition of the arenediazonium tetrafluoroborate **11a−n** (0.25 mmol). The reaction was stirred at room temperature with the reaction progress monitored by the evolution of N_2. After nitrogen ceased bubbling, the reaction mixture was loaded directly onto a silica gel column and flash chromatographed using hexanes/ethyl acetate (9:1) as eluent to give the desired Heck adducts as homogeneous materials (single spot on TLC). Except when noted, the products were obtained as clean pale yellow oils. Note: The physical conditions of the base NaOAc is crucial to attain good yields in the Heck−Matsuda reactions. The NaOAc has limited solubility in benzonitrile, and its use as a fine powder is recommended.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-*p*-tolylcyclopent-2-enecarboxylate-11a.** 90% yield (75 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.10 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6, 2H), 5.98 (dd, J = 1.9 and 5.5, 1H), 5.81 (dd, J = 2.2 and 5.2, 1H), 4.03 (tt, J = 2.2 and 7.7, 1H), 3.72 (s, 3H), 3.31 (dd, peak underneath residual CD_3OD, 1H), 2.38 (s, 3H), 1.76 (dd, J = 7.4 and 13.5, 1H), 1.42 (s, 9H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.6, 157.6, 142.7, 141.0, 137.4, 132.1, 130.4, 128.4, 80.8, 72.39, 53.1, 50.2, 47.7, 28.9, 21.2; HRMS calcd for ($C_{19}H_{25}NO_4Na$) 354.1681, found 354.1658.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-ethylphenyl)cyclopent-2-enecarboxylate-11b.** 56% yield (48 mg): ^{1}H NMR CD_3OD, 500 MHz, δ (ppm) 7.10 (s, 4H), 6.00 (dd, J = 1.9 and 5.4, 1H), 5.83 (bs, 1H), 4.04 (tt, J = 2.2 and 7.9, 1H), 3.70 (s, 3H), 3.23 (dd, J = 8.2 and 13.5, 1H), 2.55 (q, J = 7.6, 2H), 1.77 (dd, J = 7.4 and 13.5, 1H), 1.43 (s, 9H), 1.22 (t, J = 7.5, 3H); ^{13}C NMR CD_3OD, 150 MHz, δ (ppm) 175.6, 157.7, 144.0, 143.0, 141.0, 132.1, 129.2, 128.5, 80.7, 72.3, 53.1, 51.9, 47.6, 29.6, 28.9, 16.4; HRMS calcd for ($C_{20}H_{27}NO_4Na$) 368.1838, found 368.1851.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-propylphenyl)cyclopent-2-enecarboxylate- 11c.** 90% yield (75 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.10 (s, 4H), 6.00 (dd, J = 1.9 and 5.4, 1H), 5.83 (dd, J = 2.0 and 5.2, 1H), 4.04 (tt, J = 2.2 and 7.9, 1H), 3.70 (s, 3H), 3.23 (dd, J = 8.2 and 13.5, 1H), 2.55 (t, J = 7.6, 2H), 1.77 (dd, J = 7.4 and 13.5, 1H), 1.61 (sx, J = 7.5, 2H), 1.42 (s, 9H), 0.92 (t, J = 7.4, 3H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.6, 157.7, 143.1, 142.3, 141.0, 132.1, 129.8, 128.4, 80.7, 72.4, 53.1, 51.9, 47.5, 38.8, 28.9, 25.9, 14.2; HRMS calcd for ($C_{21}H_{29}NO_4H$) 360.2175, found 360.2159.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-butylphenyl)cyclopent-2-enecarboxylate-11d.** 71% yield (66 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.10 (s, 4H), 5.99 (dd, J = 1.9 and 5.4, 1H), 5.84 (dd, J = 2.0 and 5.2, 1H), 4.00 (tt, J = 2.0 and 7.7, 1H), 3.72 (s, 3H), 3.28 (peak underneath residual CD_3OD, 1H), 2.57 (t, J = 7.6, 2H), 1.77 (dd, J = 7.4 and 13.5, 1H), 1.57 (qn, J = 7.6, 2H), 1.42 (s, 9H), 1.34 (sx, J = 7.7, 2H), 0.90 (t, J = 7.3, 3H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.6, 157.6, 143.0, 142.4, 141.0, 132.1, 129.9, 128.4, 80.7, 72.3, 53.1, 51.9, 47.6, 36.4, 35.1, 28.9, 23.5, 14.4; HRMS calcd for ($C_{22}H_{31}NO_4H$) 374.2331, found 374.2326.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-pentylphenyl)cyclopent-2-enecarboxylate-11e.** 80% yield (78 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.09 (s, 4H), 5.97 (dd, J = 1.9 and 5.4, 1H), 5.82 (dd, J = 2.0 and 5.2, 1H), 3.71 (s, 3H), 4.04 (t, J = 7.4, 1H), 3.29 (dd, J = 8.4 and 13.4, 1H), 2.55 (t, J = 7.7, 2H), 1.77 (dd, J = 7.0 and 13.4, 1H), 1.58 (qn, J = 7.0, 2H), 1.41 (s, 9H), 1.30 (m, 4H), 0.89 (t, J = 7.0, 3H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.5, 157.5, 142.9, 142.4, 141.0, 132.1, 129.8, 128.4, 80.6, 72.3, 53.1, 51.9, 47.6, 36.6, 32.7, 32.6, 28.9, 23.7, 14.6; HRMS calcd for ($C_{23}H_{33}NO_4H$) 388.2488, found 388.2492.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-hexylphenyl)cyclopent-2-enecarboxylate-11f.** 85% yield (85 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.09 (s, 4H), 5.97 (dd, J = 1.9 and 5.4, 1H), 5.82 (dd, J = 2.0 and 5.2, 1H), 4.04 (tt, J = 2.0 and 7.4, 1H), 3.71 (s, 3H), 3.29 (peak underneath residual CD_3OD, 1H), 2.56 (t, J = 7.3, 2H), 1.78 (dd, J = 7.5 and 13.6, 1H), 1.58 (qn, J = 7.7, 2H), 1.41 (s, 9H), 1.30 (m, 6H), 0.88 (t, J = 6.7, 3H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.6, 157.6, 143.0, 142.4, 141.0, 132.1, 129.8, 128.4, 80.7, 72.4, 53.1, 51.9, 47.6, 36.7, 33.0, 32.9, 30.2, 28.9, 23.2, 14.6; HRMS calcd for ($C_{24}H_{35}NO_4H$) 402.2644, found 402.2674.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-heptylphenyl)cyclopent-2-enecarboxylate-11g.** 78% yield (81 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.09 (s, 4H), 5.98 (dd, J = 2.0 and 5.4, 1H), 5.82 (bs, 1H), 4.04 (m, 1H), 3.72 (s, 3H), 3.30 (peak underneath residual CD_3OD, 1H), 2.55 (t, J = 7.5, 2H), 1.78 (dd, J = 7.6 and 13.7, 1H), 1.42 (s, 9H), 1.57 (m, 2H), 1.30 (m, 8H), 0.89 (m, 3H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.5, 157.5, 142.9, 142.5, 141.0, 132.1, 129.8, 128.4, 80.6, 72.3, 53.1, 51.9, 47.6, 36.7, 33.1, 32.9, 30.4, 30.4, 28.9, 23.8, 14.6; HRMS calcd for ($C_{25}H_{37}NO_4H$) 416.2797, found 416.2801.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-octylphenyl)cyclopent-2-enecarboxylate-11h.** 90% yield (97 mg): ^{1}H NMR DMSO-d_6, 500 MHz, δ (ppm) 7.75 (s, 1H), 7.12 (d, J = 8.5, 2H), 7.08 (d, J = 8.5, 2H), 5.97 (dd, J = 1.5 and 5.5, 1H), 5.83 (d, J = 3, 1H), 3.95 (t, J = 7.5, 1H), 3.61 (s, 3H), 3.09 (dd, J = 8.5 and 13.5, 1H), 2.51 (t, J = 7.5, 2H), 1.71 (dd, J = 7.5 and 13.5, 1H), 1.53 (qn, J = 7.5, 2H), 1.36 (s, 9H), 1.25 (m, 10H), 0.85 (t, J = 7.5, 3H); ^{13}C NMR DMSO-d_6, 125 MHz, δ (ppm) 174.0, 155.8, 142.2, 141.1, 139.2, 132.1, 129.1, 127.8, 127.7, 79.0, 71.0, 55.6, 50.1, 46.4, 35.5, 32.0, 31.7, 29.5, 29.4, 29.4, 22.4, 14.9; ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.09 (s, 4H), 5.98 (dd, J = 2 and 5.4, 1H), 5.82 (dd, J = 2.3 and 5.3, 1H), 4.03 (tt, J = 2 and 7.8, 1H), 3.71 (s, 3H), 3.29 (dd, J = 8.3 and 13.3, 1H), 2.55 (t, J = 7.5, 2H), 1.78 (dd, J = 7.5 and 13.5, 1H), 1.57 (qn, J = 7, 2H), 1.41 (s, 9H), 1.28 (bs, 10H), 0.88 (t, J = 7.5, 3H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.5, 157.6, 143.0, 142.4, 141.0, 132.1, 129.8, 128.4, 80.6, 72.3, 53.1, 51.9, 47.6, 36.7, 33.2, 32.9, 30.7, 30.5, 30.5, 28.9, 23.8, 14.6; HRMS calcd for ($C_{26}H_{39}NO_4H$) 430.2957, found 430.2932.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-iodophenyl)cyclopent-2-enecarboxylate-11i.** 58% yield (64 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.64 (d, J = 8.4, 2H), 7.00 (d, J = 8.4, 2H), 6.00 (*dd*, J = 2.0 and 5.5, 1H), 5.86 (*dd*, J = 2.4 and 5.5, 1H), 4.05 (t, J = 7.8, 1H), 3.72 (s, 3H), 3.31 (dd, peak underneath residual CD_3OD, 1H), 1.76 (dd, J = 7.5 and 13.7, 1H), 1.42 (s, 9H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.2, 157.4, 145.5, 140.0, 138.8, 132.8, 130.7, 92.5, 80.6, 72.2, 53.2, 51.6, 47.2, 28.9; HRMS calcd for ($C_{18}H_{22}INO_4Na$) 466.0491, found 466.0474.

***rac*-(1*S**,4*R**)-*tert*-Butyl-1-(*tert*-butoxycarbonylamino)-4-(4-iodophenyl)cyclopent-2-enecarboxylate-11j.** 41% yield (50 mg): ^{1}H NMR DMSO-d_6, 500 MHz, δ (ppm) 7.7 (d, J = 8, 2H), 7.00 (d, J = 8.3 Hz, 2H), 5.92 (d, J= 6.0, 1H), 5.83 (bs, 1H), 3.95 (t, J = 7.5, 1H), 3.13 (dd, J = 8.3 and 13.5, 1H), 1.62 (dd, J = 7.3 and 13.5, 1H), 1.38 (bs, 18H); ^{13}C NMR DMSO-d_6, 62.5 MHz, δ (ppm) 172.4, 156.1, 144.3, 138.2, 137.4, 131.7, 129.2, 81.0, 78.9, 71.3, 50.4, 45.6, 27.4, 26.8; HRMS calcd for ($C_{21}H_{28}NO_4IH$) 486.1121, found 486.1141. Obtained as a white solid after flash chromatography, mp 144−145 °C.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(2,4-dimethoxyphenyl)cyclopent-2-enecarboxylate-11k.** 70% yield (66 mg): ^{1}H NMR CD_3OD, 500 MHz, δ (ppm) 6.98 (d, J = 8.3, 1H), 6.49 (d, J = 2.3, 1H), 6.45 (dd, J = 2.5 and 8.3, 1H), 5.98 (dd, J = 2.4 and 5.4, 1H), 5.81 (bs, 1H), 4.35 (tt, J = 2.2 and 7.4, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.23 (dd, J = 8.2 and 13.5, 1H), 1.68 (dd, J = 7.2 and 13.5, 1H), 1.41 (s, 9H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.7, 161.3, 159.3, 157.6, 140.8, 131.7, 128.9, 126.1, 105.8, 99.4, 80.6, 72.2, 56.0, 55.9, 53.1, 46.2, 44.6, 28.9; HRMS calcd for ($C_{20}H_{27}NO_6H$) 378.1917, found 378.1921.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(2,5-dimethoxyphenyl)cyclopent-2-enecarboxylate-11l.** 65% yield (61 mg): ^{1}H NMR CD_3OD, 500 MHz, δ (ppm) 6.85 (d, J = 9.0,

dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182−8190

1H), 6.73 (dd, J = 3.0 and 9.0, 1H), 6.69 (dd, J = 2.4 and 8.3, 1H), 6.00 (dd, J = 2.0 and 5.5, 1H), 5.85 (bs, 1H), 4.41 (tt, J = 2.1 and 7.6, 1H), 3.78 (s, 3H), 3.72 (s, 6H), 3.26 (dd, J = 8.2 and 13.5, 1H), 1.72 (dd, J = 7.2 and 13.5, 1H), 1.41 (s, 9H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.7, 157.6, 155.5, 152.7, 140.3, 135.0, 132.3, 115.0, 113.0, 112.9, 80.6, 72.2, 56.7, 56.2, 53.1, 46.0, 45.0, 28.9; HRMS calcd for ($C_{20}H_{28}NO_6$) 378.1917, found 378.1933.

***rac*-(1*S**,4*R**)-*tert*-Butyl-1-(*tert*-butoxycarbonylamino)-4-(2,5-dimethoxyphenyl)cyclopent-2-enecarboxylate-11m.** 40% yield (42 mg): ^{1}H NMR CD_3OD, 500 MHz, δ (ppm) 6.89 (d, J = 8.7, 1H), 6.73 (dd, J = 3.0 and 8.6, 1H), 6.69 (m, 1H), 6.00 (d, J = 5.5, 1H), 5.83 (bs, 1H), 4.42 (t, J = 7.5, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.24 (dd, J = 8.3 and 13.5, 1H), 1.67 (dd, J = 7.0 and 13.5, 1H), 1.47 (s, 9H), 1.43 (s, 9H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 174.3, 157.4, 155.5, 152.7, 140.0, 139.7, 135.3, 132.7, 114.9, 112.9, 82.4, 72.8, 56.8, 56.2, 45.8, 45.2, 44.4, 28.9, 28.3; HRMS calcd for ($C_{23}H_{33}NO_6Na$) 442.2206, found 442.2192.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(3,4-dimethoxyphenyl)cyclopent-2-enecarboxylate-11n.** 90% yield (85 mg): ^{1}H NMR CD_3OD, 600 MHz, δ (ppm) 6.88 (d, J = 8.1, 1H), 6.82 (s, 1H), 6.75 (dd, J = 2.0 and 8.1, 1H), 6.00 (dd, J = 2.0 and 5.5, 1H), 5.83 (bs, 1H), 4.02 (tt, J = 2.1 and 7.6, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (s, 6H), 3.26 (m, 1H), 1.80 (dd, J = 7.0 and 13.6, 1H), 1.42 (s, 9H), ^{13}C NMR CD_3OD, 150 MHz, δ (ppm) 175.6, 157.6, 150.8, 149.4, 141.0, 138.8, 132.1, 120.8, 113.3, 112.4, 80.6, 72.3, 56.7, 56.6, 53.1, 51.9, 47.3, 28.9; HRMS calcd for ($C_{20}H_{28}NO_6$) 378.1917, found 378.1921.

***rac*-(1*S**,4*R**)-*tert*-Butyl-1-(*tert*-butoxycarbonylamino)-4-(2,5-dimethoxyphenyl)cyclopent-2-enecarboxylate-11o.** 64% yield (67 mg): ^{1}H NMR DMSO-d_6, 250 MHz, δ (ppm) 6.87 (d, J = 8.3, 1H), 6.75 (s, 1H), 6.66 (dd, J = 1.8 and 8.3, 1H), 5.92 (dd, J = 1.8 and 5.5, 1H), 5.77 (d, J = 3.3, 1H), 3.90 (t, J = 7.5, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.06 (dd, J = 8.0 and 13.3, 1H), 1.65 (dd, J = 7.3 and 13.5, 1H), 1.37 (s, 18H); ^{13}C NMR DMSO-d_6, 62.5 MHz, δ (ppm) 172.2, 170.6, 155.3, 149.2, 147.8, 138.8, 137.5, 133.2, 132.1, 119.4, 112.4, 111.6, 78.4, 71.3, 56.0, 55.8, 45.9, 28.6, 28.0; HRMS calcd for ($C_{23}H_{33}NO_6H$) 420.2386, found 420.2371.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-[4-(benzyloxycarbonylamino)phenyl]cyclopent-2-enecarboxylate-11p.** 70% yield (82 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.32 (m, 7H), 7.12 (d, J = 8.5, 2H), 5.98 (dd, J= 2.3 and 5.0, 1H), 5.82 (*d*, J= 3.5, 1H), 5.16 (s, 2H), 4.03 (t, J = 7.0, 1H), 3.71 (s, 3H), 3.30 (dd, J = 8.2, 1H), 1.76 (dd, J = 7.5 and 13.5, 1H), 1.41 (s, 9H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 174.5, 174.3, 154.7, 138.7, 137.5, 137.0, 128.3, 127.9, 127.8, 127.6, 127.6, 118.8, 79.4, 71.0, 66.3, 51.8, 50.4, 49.5, 46.2, 27.5; HRMS calcd for ($C_{26}H_{30}N_2O_6K$) 505.1741, found 505.1760. Obtained as a white solid after flash chromatography, mp 152−153 °C.

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-(4-cyanophenyl)cyclopent-2-enecarboxylate-11q.** 69% yield (59 mg): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.67 (d, J = 8.4, 2H), 7.41 (d, J = 8.2, 2H), 6.03 (*dd*, J = 1.9 and 5.5, 1H), 5.91 (*dd*, J = 2.2 and 5.4, 1H), 4.18 (tt, J = 2.11 and 7.7, 1H), 3.72 (s, 3H), 3.35 (dd, peak underneath residual CD_3OD, 1H), 1.79 (dd, J = 7.2 and 13.6, 1H), 1.41 (s, 9 H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 175.2, 157.5, 151.7, 139.4, 133.7, 133.6, 129.7, 119.9, 111.6, 80.8, 72.4, 53.2, 52.2, 47.0, 28.8; HRMS calcd for ($C_{19}H_{23}N_2O_4$) 343.1652, found 343.1658.

***rac-tert*-Butyl-(1*S**,4*R**)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-enylcarbamate-13a.** A solution of **11h** (0.080 g, 0.19 mmol) in THF/EtOH (0.6 mL/1 mL) was placed in a round bottomed flask. To this solution was added dry $CaCl_2$ (0.063 g; 0.57 mmol), and after complete dissolution of $CaCl_2$, $NaBH_4$ (0.049; 0.13 mmol) was introduced at once. The mixture was stirred at room temperature for 5 h when a solution of 2 M K_2CO_3 (1.2 mL) was added. Next, saturated $NaHCO_3$ (1.2 mL) was added, and the organic phase was extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, dried with Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent, providing the alcohol **13a** in 80% yield (0.061 g) and the minor diastereoisomer **13b** in (0.002 g; 3% yield): ^{1}H NMR DMSO-d_6, 500 MHz, δ (ppm) 7.11 (dd, 8.5, 2H), 7.09 (dd, J = 8.5, 2H), 6.62 (bs, 1H), 5.88 (dd, J = 2 and 5.5, 1H), 5.74 (dd, J = 1.5 and 5.5, 1H), 4.76 (t, J = 6, 1H), 3.76 (tt, J = 2 and 6, 1H), 3.46 (dd, J = 6.5 and 11, 1H), 3.41 (dd, J = 6 and 10.5, 1H), 2.51 (t, J = 8, 2H), 2.50 (dd, peak underneath residual DMSO, 1H), 1.71 (dd, J = 7.5 and 12, 1H), 1.53 (qn, J = 7, 2H), 0.85 (t, J = 7.5, 3H), 1.37 (s, 9H), 1.25 (m, 10H), ^{13}C NMR DMSO-d_6, 125 MHz, δ (ppm) δ 154.2, 142.6, 140.0, 135.0, 134.8, 128.2, 127.1, 77.5, 68.7, 65.0, 48.8, 43.1, 34.8, 31.2, 31.0, 28.8, 28.7, 28.6, 28.3, 22.0, 13.9; HRMS calcd for ($C_{25}H_{39}NO_3H$) 402.3008, found 402.3011. Obtained as a white solid after flash chromatography, mp 142−143 °C.

***rac-tert*-Butyl-(1*R**,4*R**)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-enylcarbamate-13b.** ^{1}H NMR DMSO-d_6, 500 MHz, δ (ppm) 7.09 (d, J = 8.5, 2H), 7.06 (d, J = 8.5, 2H), 6.60 (bs, 1H), 5.79 (dd, J = 1.5 and 5.5, 1H), 4.76 (t, J = 6, 1H), 4.00 (t, J = 7.5, 1H), 3.53 (dd, J = 6 and 10.5, 1H), 3.42 (dd, J = 6 and 10.5, 1H), 2.50 (t, peak underneath residual DMSO, 1H), 3.42 (dd, J = 6 and 10.5, 1H), 2.42 (dd, J = 8.5 and 13.5, 1H), 1.72 (dd, J = 7 and 13.5, 1H), 1.53 (qn, J = 7, 2H), 1.37 (s, 9H), 1.25 (m, 10H), 0.85 (t, J = 7, 3H); ^{13}C NMR CD_3OD, 150 MHz, δ (ppm) 157.5. 143.8, 142.1, 139.2, 134.6, 129.7, 128.3, 80.0, 70.8, 68.0, 51.2, 44.1, 36.7, 33.2, 33.0, 30.7, 30.6, 30.5, 29.0, 23.9, 14.6; HRMS calcd for ($C_{25}H_{39}NO_3H$) 402.3008, found 402.3021. Obtained as a white solid after flash chromatography, mp 92−93 °C.

***rac-tert*-Butyl-(1*R**,3*S**)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentylcarbamate-14.** A suspension of the alcohol **13a** (0.090 g, 0.22 mmol) and Pd/C (5%) (0.024 g; 0.01 mmol) in methanol (2 mL), was stirred for 6 h under hydrogen (balloon). Next, the mixture was filtered through a plug of silica and concentrated under reduced pressure to provide the reduced product **14** in 0.080 g as a colorless oil (90% yield). Spectroscopic data were in accordance with the literature:[14b] ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 7.14 (d, J = 8.3, 2H), 7.10 (d, J = 8.3, 2H), 4.83 (s, 1H), 3.72 (m, 2H), 3.31 (m, 1H), 2.56 (t, J = 7.5, 2H), 2.41 (dd, J = 7.7 and 13.5, 1H), 2.09 (m, 2H), 1.96−1.49 (m, 7H), 1.43 (s, 9H), 1.28 (m, 10H), 0.88 (t, J = 6.5, 3H); ^{1}H NMR CD_3OD, 600 MHz, δ (ppm) 7.15 (d, J = 8.0, 2H), 7.06 (d, J = 8.0, 2H), 3.66 (d, J = 11.0, 1H), 3.62 (d, J = 11.0, 1H), 3.04 (m, 1H), 2.55 (t, J = 7.7, 2H), 2.23 (dd, J = 7.8 and 13.3, 1H), 2.01 (m, 2H), 1.89 (m, 2H), 1.82 (m, 1H), 1.58 (qn, J = 7.1), 1.45 (s, 9H), 1.30 (m, 10H), 0.89 (t, J = 7.1, 3H); ^{13}C NMR CD_3OD, 150 MHz, δ (ppm) 157.6, 143.7, 141.7, 129.5, 128.1, 80.0, 67.5, 65.3, 45.8, 44.3, 36.7, 36.4, 34.65, 33.2, 33.0, 30.7, 30.6, 30.5, 29.0, 23.9, 14.6; HRMS calcd for ($C_{25}H_{41}NO_3H$) 404.3165, found 404.3180.

***rac-tert*-Butyl-(1*S**,3*S**)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentylcarbamate-14b.**[14b] Obtained by the hydrogenation of 2 mg of **13b**. Spectroscopic data were in accordance with the literature:[14b] ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 7.14 (d, J = 8.3, 2H), 7.10 (d, J = 8.3, 2H), 4.83 (s, 1H), 3.77 (d, J = 11.8, 1H), 3.70 (d, J = 11.8, 1H), 3.31 (m, 1H), 2.56 (t, J = 7.5, 2H), 2.31 (dd, J = 7.7 and 13.5, 1H), 2.10 (m, 2H), 1.85−1.50 (m, 7H), 1.45 (s, 9H), 1.26 (m, 10H), 0.88 (t, J = 6.5, 3H).

***rac*-(1*S**,4*R**)-Methyl-1-(*tert*-butoxycarbonylamino)-4-[4-(oct-1-ynyl)phenyl]cyclopent-2-enecarboxylate-17.** To a suspension of the iodide **11i** (0.130 g; 0.29 mmol), CuI (0.0033 g; 0.0174 mmol; 6 mol %) and $Pd(PPh_3)_4$ (0.0067 g; 0.0058 mmol; 2 mol %), in dry triethylamine (3.2 mL), under nitrogen, was added 1-octyne (0.064 g; 0.086 mL; 0.58 mmol). The yellow colored mixture was stirred at room temperature for 3 h. Next, the solvent was evaporated, and the resulting brown residue was dissolved in 10 mL of EtOAc and washed with 3 × 5 mL of saturated solution of NH_4Cl. The organic phase was evaporated, and the crude mixture purified by column chromatography [dichloromethane:methanol (99:1) as eluent] to give **17** in 85% yield (0.103 g): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.29 (d, J = 8.2, 2H), 7.14 (d, J = 8.2, 2H), 5.99 (dd, J = 1.9 and 5.5, 1H), 5.85 (dd, J = 2.2 and 5.4, 1H), 4.01 (tt, J = 7.8, 1H), 3.72 (s, 3H), 3.31 (peak underneath residual CD_3OD, 1H), 2.37 (t, J = 6.9, 2H), 1.77 (dd, J = 7.4 and 13.3, 1H), 1.50 (m, 8H), 1.42 (s, 9H), 0.92 (t, J = 6.7, 3H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 175.4, 157.6, 145.3,

dx.doi.org/10.1021/jo3015209 | J. Org. Chem. 2012, 77, 8182−8190

140.4, 132.9, 132.7, 128.5, 124.0, 90.8, 80.7, 72.3 53.1, 52.1, 47.3, 32.7, 33.1, 29.8, 28.9, 28.8, 23.8, 20.1, 14.6; HRMS calcd for ($C_{26}H_{35}NO_4Na$) 448.2464, found 448.2486.

***rac*-(1*R**,3*S**)-Methyl-1-(*tert*-butoxycarbonylamino)-3-(4-octylphenyl)cyclopentanecarboxylate-18.** A suspension of the enyne **17** (0.10 g, 0.24 mmol) and Pd/C (5%) (0.024 g; 0.01 mmol) in methanol (2 mL), was stirred for 9 h under hydrogen (balloon). Next, the mixture was filtered through a plug of silica and concentrated under reduced pressure to provide 0.098 g of the reduced product **18** (95% yield): ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.15 (d, J = 8.2, 2H), 7.07 (d, J = 8.2, 2H), 3.22 (m, 1H), 3.72 (s, 3H), 2.74 (dd, J = 8.2 and 13.4, 1H), 2.55 (t, J = 7.3, 1H), 2.29 (m, 1H), 2.10 (m, 2H), 1.90 (m, 2H), 1.74 (m, 1H), 1.43 (s, 9H), 1.58 (m, 2H), 1.29 (bs, 10H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR CD_3OD, 125 MHz, δ (ppm) 177.4, 157.9, 142.9, 142.0, 129.6, 128.1, 80.6, 67.0, 53.0, 47.0, 46.1, 36.7, 34.9, 33.2, 32.9, 30.7, 30.5, 30.5, 28.9, 25.4, 23.9, 14.6; HRMS calcd for ($C_{26}H_{41}NO_4H$) 432.3114, found 432.3116.

***rac*-[(1*R**,3*S**)-1-Amino-3-(4-octylphenyl)cyclopentyl]-methanol (VPC01091)-15.** Prepared according to the literature:[14b] ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.21 (d, J = 8.0, 2H). 7.11 (d, J = 8.0, 2H), 3.67 (d, J= 11.5, 1H), 3.59 (d, J= 11.5, 1H), 2.57 (t, J = 7.4, 1H), 3.14 (m, 1H), 2.43 (dd, J = 7.0 and 13.4, 1H), 2.16 (m, 1H), 1.94 (m, 3H), 1.73 (m, 1H), 1.59 (m, 2H), 1.29 (bs, 10H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 141.9. 140.6, 128.3, 126.7, 44.5, 35.5, 33.0, 31.8, 31.5, 29.4, 29.4, 29.2, 22.6, 14.0; HRMS calcd for ($C_{20}H_{33}NOH$) 304.2640, found 304.2625.

***rac*-[(1*R**,3*S**)-1-Amino-3-(4-octylphenyl)cyclopentyl]-methanol hydrochloride (VPC01091)-16.** Prepared according to the literature:[14b] ^{1}H NMR CD_3OD, 250 MHz, δ (ppm) 7.21 (d, J = 8.0, 2H). 7.10 (d, J = 8.0, 2H), 3.67 (d, J= 11, 1H), 3.61 (d, J= 11, 1H), 3.11 (m, 1H), 2.74 (dd, J = 8.2 and 13.4, 1H), 2.53 (t, J = 7.3, 1H), 2.43 (dd, J = 6.9 and 13.3, 1H), 1.95 (m, 5H), 1.57 (m, 2H), 1.29 (bs, 10H), 0.88 (t, J = 6.9, 3H); ^{13}C NMR CD_3OD, 62.5 MHz, δ (ppm) 142.6, 141.9, 130.0, 128.3, 65.8, 45.9, 43.4, 37.0, 34.8, 34.1, 33.5, 33.2, 31.0, 30.9, 30.8, 24.2, 15.0; HRMS calcd for ($C_{20}H_{33}NOH$) 304.2640, found 304.2664.

Chemoselective Reduction of the Enyne 17. A suspension of the enyne **17** (0.050 g, 0.118 mmol) and PtO_2 (0.0012 g; 0.0059 mmol) in methanol (2 mL) was stirred for 8 h under hydrogen (balloon). Next, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography [hexane:ethyl acetate (9:1)] to provide **11h** in 0.040 g (78% yield).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Determination of the diastereomeric ratio of the Heck products, data regarding the reduction of enyne **17**, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: roque@iqm.unicamp.br.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Research Supporting Foundation of the State of São Paulo (FAPESP), the Brazilian National Research Council (CNPq), and the Coordination for the Improvement of Higher Education Level Personnel (Capes) for financial support and fellowships.

■ REFERENCES

(1) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002. (d) Tsuji, J. *Palladium Reagents and Catalyst*; Wiley: Chichester, U.K., 2004. (e) *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, U.K., 2009.

(2) (a) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622. (b) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403. (c) Felpin, F.-X.; Nassar-Hardy, L.; Callonnec, F. L.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815.

(3) Moro, A. V.; Cardoso, F. S. P.; Correia, C. R. D. *Org. Lett.* **2009**, *11*, 3642.

(4) Prediger, P.; Barbosa, L. F.; Génisson, Y.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 7737.

(5) The term substrate-directable Heck–Matsuda reaction was inspired by the seminal review of Evans, Hoveyda and Fu in the early 90's and is related to a pre-associative interaction of the reagent with polar functional groups neighboring the reaction center, which directly influence the stereoselectivity of the overall process: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(6) For an example of a similar olefin used in a substrate-directable reaction see: Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815.

(7) Stewart, C.; Keitz, B. K.; Kuhn, K. M.; Thomas, R. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 8534.

(8) Niwayama, S.; Cho, H.; Lin, C. *Tetrahedron Lett.* **2008**, *49*, 4434.

(9) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *7*, 4107.

(10) (a) Soldi, C.; Moro, A. V.; Pizzolatti, M. G.; Correia, C. R. D. *Eur. J. Org. Chem.* **2012**, 3607. (b) Nassar-Hardy, L.; Fabre, S.; Amer, A. M.; Fouquet, E.; Felpin, F.-X. *Tetrahedron Lett.* **2012**, *53*, 338. (c) Schwalm, C. S.; de Castro, I. B. D.; Ferrari, J.; de Oliveira, F. L.; Aparício, R.; Correia, C. R. D. *Tetrahedron Lett.* **2012**, *53*, 1660. (d) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692. (e) Taylor, J. G.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 857. (f) da Penha, E. T.; Forni, J. A.; Biajoli, A. F. P.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 6342. (g) Schmidt, B.; Holter, F.; Kelling, A.; Schilde, U. *J. Org. Chem.* **2011**, *76*, 3357. (h) Taylor, J. G.; Ribeiro, R. S.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 3861. (i) de Azambuja, F.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 42. (j) Siqueira, F. A.; Taylor, J. G.; Correia, C. R. D. *Tetrahedron Lett.* **2010**, *51*, 2102. (k) For an enantioselective version of the Heck–Matsuda reaction, see: Correia, C. R. D.; Oliveira, C. C.; Salles, A. G., Jr.; dos Santos, E. A. F. *Tetrahedron Lett.* **2012**, *53*, 3325.

(11) (a) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159. (b) Kikukawa, K.; Maemura, K.; Nagira, K.; Wada, F.; Matsuda, T. *Chem. Lett.* **1980**, 551. (c) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (d) Sengupta, S.; Bhattacharya, S. *J. Chem. Soc. Perkin Trans. 1* **1993**, *17*, 1943. (e) Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1999**, 1357. (f) Salabert, J.; Sebstián, R. M.; Vallribera, A.; Roglans, A.; Nájera, C. *Tetrahedron.* **2011**, *45*, 8659. (g) Pla-Quintana, A.; Parella, T.; Roglans, A. *Adv. Synth. Catal.* **2011**, *353*, 2003.

(12) (a) Artuso, E.; Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Tetrahedron* **1981**, *37*, 31. (b) Nelson, M. L.; Ismail, M. Y.; McIntyre, L.; Bhatia, B.; Viski, P.; Hawkins, P.; Rennie, G.; Andorsky, D.; Messersmith, D.; Stapleton, K.; Dumornay, J.; Sheahan, P.; Verma, A. K.; Warchol, T.; Levy, S. B. *J. Org. Chem.* **2003**, *68*, 5838. (c) Peñafiel, I.; Pastor, I. M.; Yus, M. *Eur. J. Org. Chem.* **2012**, 3151.

(13) The assignment of the H_1 as the more shielded hydrogen was based on precedents reported for similar cyclopentenes. For examples, see: (a) Larue, V.; Gharbi-Benarous, J.; Acher, F.; Valle, G.; Crisma, M.; Toniolo, C.; Azerad, R.; Girault, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1111. (b) Ung, A. T.; Pyne, S. G.; Batenburg-Nguyen, U.; Davis, A. S.; Sherif, A.; Biscoff, F.; Lesage, A. S. J. *Tetrahedron* **2005**, *61*, 1803.

(14) (a) Lynch, K. R.; Macdonald, T. L. Sphingosine 1-Phosphate Agonists Comprising Cycloalkanes and 5-Membered Heterocycles Substituted by Amino and Phenyl Groups. WO Patent 2006088944, 2006. (b) Zhu, R.; Snyder, A. H.; Kharel, Y.; Schaffter, L.; Sun, Q.; Kennedy, P. C.; Lynch, K. R.; Macdonald, T. L. *J. Med. Chem.* **2007**, *50*, 6428. (c) Fix-Stenzel, S. R.; Hayes, M. E.; Zhang, X.; Wallace, G. A.; Grongsaard, P.; Schaffter, L. M.; Hannick, S. M.; Franczyk, T. S.;

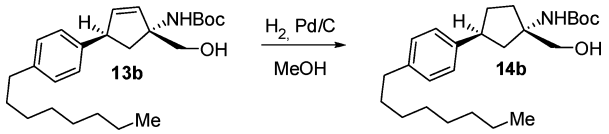
Stoffel, R. H.; Cusack, K. P. *Tetrahedron Lett.* **2009**, *50*, 4081. (d) Wallace, G. A.; Gordon, T. D.; Hayes, M. E.; Konopacki, D. B.; Fix-Stenzel, S. R.; Zhang, X.; Grongsaard, P.; Cusack, K. P.; Schaffter, L. M.; Henry, R. F.; Stoffel, R. H. *J. Org. Chem.* **2009**, *74*, 4886.

(15) Strader, C. R.; Pearce, C. J.; Oberlies, N. H. *J. Nat. Prod.* **2011**, *74*, 900.

(16) For a recent Heck−Matsuda reaction leading to the synthesis of a $S1P_1$ agonist, see: Nakano, T.; Miyahara, M.; Itoh, T.; Kamimura, A. *Eur. J. Org. Chem.* **2012**, 2161.

(17) (a) Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, R. J. *Synth. Commun.* **1995**, *25*, 561. (b) Moro, A. V.; Santos, M. R.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 7259.

(18) The minor diastereomer (**13b**) of the alcohol **13** was isolated by column chromatography and hydrogenated to provide the compound **14b**. The ^{1}H NMR of the cyclopentanes **14** and **14b** were identical for those reported in reference 14b.



(19) Procedure adapted from: Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453.

(20) The ^{1}H and ^{13}C NMR spectra for VPC01091 (**16**) are slightly different from those reported in reference 14c. The NMR chemical shifts for aminoalcohols might change depending on the water content in the sample and because of variations in temperature. For a representative example, see: Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

(21) See the Supporting Information for details.

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(23) Plé, K.; Haudrechy, A.; Probst, N. P. *Tetrahedron* **2010**, *66*, 5030.

(24) (a) Dunker, M. F. W.; Starkey, E. B.; Jenkins, G. L. *J. Am. Chem. Soc.* **1936**, *58*, 2308. (b) Starkey, E. B. *Org. Synth.* **1943**, *2*, 225.