Palladium-Catalyzed Tandem Allylation of *o*-Phenylenediamines Using 2-Butene-1,4-diol Directly

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*Summary: The direct activation of C−O bonds in 2-butene-1,4-diol by palladium complexes has been accelerated by carrying out the reactions in the presence of a titanium reagent. Palladium-catalyzed tandem allylation of o-phenylenediamines with 2-butene-1,4-diol leads to 1,2,3,4-tetrahydro-2-vinylquinoxalines. The cyclization of o-phenylenediamine with 2-butene-1,4-diol catalyzed by palladium acetate coordinated with (R)-BINAP as the chiral ligand leads to optically active 1,2,3,4-tetrahydro-2-vinylquinoxaline (**3a**) with 19% ee and in 58% yield.*

Introduction

Piperazine derivatives have aroused increasing interest due to their presence in a large number of therapeutically and biologically active compounds.[1] Numerous quinoxaline derivatives have been prepared to get biologically active compounds, and the research continues to synthesize new compounds having unusual skeletons.[2] A principal goal of organometallic chemistry is the catalytic synthesis of organic compounds by using the distinct reaction chemistry of organic ligands covalently bound to transition metals. Most organometallic chemistry has focused on complexes with covalent metal−carbon or metal−hydrogen bonds. Transition metal η^3-allyl complexes, as well as transition metal σ-alkyl complexes, play important roles as active species and key intermediates in many reactions catalyzed by transition metal complexes.[3] The palladium-catalyzed allylation of nucleophiles is an established, efficient, and highly stereo- and chemoselective method, which has been widely applied to organic chemistry.[4] The catalytic cycle requires the formation of the cationic η^3-allylpalladium(II) complex, an intermediate that is generated by oxidative addition of allylic compounds including allylic halides,[5] acetates,[6] and carbonates[7] to a Pd(0) complex and which can be attacked by nucleophiles at both termini of the allylic system. However, there are few reports on palladium(0)-catalyzed reaction of bifunctional allylic diacetates and dicarbonates with nu-

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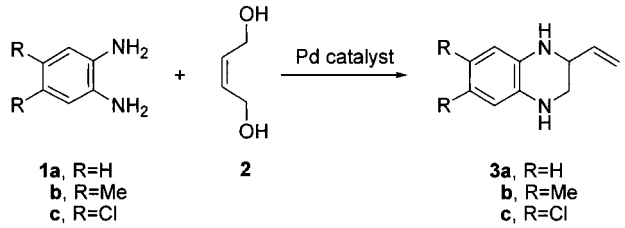
Scheme 1



1a, R=H
b, R=Me
c, R=Cl

2

3a, R=H
b, R=Me
c, R=Cl

cleophiles featuring their bifunctionality.[8] Recently, it was reported by Massacret that (*Z*)-1,4-bis(methoxycarbonyloxy)but-2-ene reacted with unprotected *o*-phenylenediamine in the presence of a palladium catalyst could not give 1,2,3,4-tetrahydro-2-vinylquinoxaline directly.[9] However, there have been only limited and sporadic reports dealing with the direct cleavage of the C−O bond of allylic alcohols on interaction with a transition metal complex.[10] Successful applications using allylic alcohols directly in catalytic processes are even more limited. This apparently stems from the poor capability of a nonactivated hydroxyl to serve as a leaving group.[11] In preliminary papers,[12] we have recently reported our attempts and some successful applications of a process involving the C−O bond cleavage with direct use of allylic alcohols catalyzed by palladium complexes. This result prompted us to study the extension of this reaction for the construction of 1,2,3,4-tetrahydro-2-vinylquinoxalines. This is, to our knowledge, the first example of palladium-catalyzed tandem allylation of *o*-phenylenediamines by the direct use of 2-butene-1,4-diol.

Results and Discussion

The palladium-catalyzed cyclization of *o*-phenylenediamines with 2-butene-1,4-diol was investigated under various conditions (Scheme 1). When a mixture of *o*-phenylenediamine (**1a**, 1 mmol) and 2-butene-1,4-diol (**2**, 0.8 mmol) was heated in the presence of catalytic amounts of $Pd(acac)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and molecular sieves (MS 4 Å) (200 mg) in benzene (5 mL) under nitrogen at 50 °C for 12 h, 1,2,3,4-tetrahydro-2-vinylquinoxaline (**3a**) was formed only in 3% yield (entry 1 in Table 1). In the reaction under reflux for 3 h, the yield of product **3a** was increased to 95% (entry 2). The reaction did not occur in the absence of the phosphine ligand (entries 3 and 15), palladium catalyst (entry 4), or titanium species (entry 5). Decreasing the amount of $Ti(OPr^i)_4$ afforded **3a** in 65% yield (entry 6). The effect of addition of $Ti(OPr^i)_4$ to promote the palladium-catalyzed allyl−OH bond cleavage remarkably enhanced both the reaction rate and yield. Titanium reagents such as $Ti(OBu)_4$ (entry 8) and $Ti(OBu^i)_4$ (entry 9) were also effective for the allylation. $Ti(OEt)_4$ (entry 7) and $Ti[O(CH_2)_{17}CH_3]_4$ (entry 10) did not so much promote the reaction. $TiCl_4$ (entry 11) could not afford **3a**. A comparative study of different catalysts in benzene was reported. As the catalyst precursor, $Pd(acac)_2$ (entry 2), $Pd(OAc)_2$ (entry 12), $PdCl_2(MeCN)_2$ (entry 16), and $Pd(OCOCF_3)_2$ (entry 17) showed high catalytic activity. Other palladium complexes such as $Pd(PPh_3)_4$ (entry 13) and $PdCl_2$ (entry 18) were less active and gave lower yield. Many reports have indicated[13] that chloride ions can strongly influence the catalytic activity of palladium catalysts, and it seemed reasonable that this factor might be responsible for the low reactivity of $PdCl_2$ in the present system. But using $Pd(PPh_3)_4$ coordinated with PPh_3 as catalyst increased the yield of product **3a** to 93% (entry 14). The presence of various monodentate ligands including PPh_3 (entry 2), $(PhO)_3P$ (entry 19), Bu_3P (entry 20), $(2\text{-}MePh)_3P$ (entry 21), $(2\text{-furyl})_3P$ (entry 22), $(2\text{-pyridyl})Ph_2P$ (entry 23), $(3\text{-}MePh)_3P$ (entry 24), $(4\text{-}MePh)_3P$ (entry 25), $(4\text{-}MeOPh)_3P$ (entry 26), $(4\text{-}FPh)_3P$ (entry 27), and $(4\text{-}ClPh)_3P$ (entry 28) showed that PPh_3, $(2\text{-furyl})_3P$, $(2\text{-pyridyl})Ph_2P$, $(4\text{-}MePh)_3P$, and $(4\text{-}MeOPh)_3P$ were the most effective ligands. The bidentate ligand including dppm (entry 29) and dppe (entry 30) decreased the yield of products. Dppp (entry 31) and dppb (entry 32) gave high yields of **3a**. The cyclization of *o*-phenylenediamine with 2-butene-1,4-diol catalyzed by palladium acetate coordinated with (*R*)-BINAP as the chiral ligand leads to optically active 1,2,3,4-tetrahydro-2-vinylquinoxaline (**3a**) with 19% ee and in 58% yield (entry 33). The use of $Pd(OAc)_2$-(*S*,*S*)-DIOP gave **3a** with lower enantioselectivities (entry 34). Compound **1b** was treated with $Pd(OAc)_2-PPh_3$ to give the cyclized product **3b** in 92% yield (entry 35). Similarly, compound **1c** gave **3c** in a yield of 70% (entry 36).

The absolute configurtion of (+)-**3a** was determined by correlation with the known compound 1,2,3,4-tetrahydro-1,4-bis(*p*-tolylsulfonyl)-2-vinylquinoxaline (**4**).[9] Compound (+)-**3a** was refluxed with tosyl chloride to give the tolyl derivative **4**, which turned out to be the *S* isomer by measurement of the optical rotation {for (+)-**4**: $[\alpha]_D^{20}$ +9.3 (*c* 4.96, $CHCl_3$); for (*R*)-**4**:[9] $[\alpha]_D^{20}$ −28.6 (*c* 0.7, $CHCl_3$) with 52% ee} (Scheme 2). The obtained compound **4** was isolated by silica gel column chromatography, and the enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralpak AD-H, eluent: *n*-hexane/2-propanol = 80:20).

A plausible reaction pathway for this reaction is shown in Scheme 2. Diol **2** or an allyl titanate, formed by an alcohol exchange reaction between **2** and isopropoxide in $Ti(OPr^i)_4$, reacts with Pd(0) species generated in situ[14] to afford the π-allylpalladium intermediate **5**.

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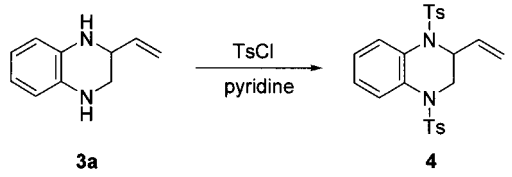
Table 1. Reaction of *o*-Phenylenediamines (1) with 2-Butene-1,4-diol (2)[a]

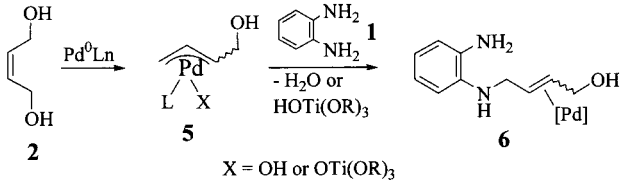
entry	1	palladium catalyst	titanium reagent	yield (%)[b] of 3
1	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OPr^i)_4$	3[c]
2	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OPr^i)_4$	95
3	**1a**	$Pd(acac)_2$	$Ti(OPr^i)_4$	0
4	**1a**	PPh_3	$Ti(OPr^i)_4$	0
5	**1a**	$Pd(acac)_2$-PPh_3		0
6	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OPr^i)_4$[d]	65
7	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OEt)_4$	74
8	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OBu)_4$	90
9	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OBu^i)_4$	94
10	**1a**	$Pd(acac)_2$-PPh_3	$Ti[O(CH_2)_{17}CH_3]_4$	45
11	**1a**	$Pd(acac)_2$-PPh_3	$TiCl_4$	0
12	**1a**	$Pd(acac)_2$-PPh_3	$Ti(OPr^i)_4$	93
13	**1a**	$Pd(PPh_3)_4$	$Ti(OPr^i)_4$	50
14	**1a**	$Pd(PPh_3)_4$-PPh_3	$Ti(OPr^i)_4$	93
15	**1a**	$PdCl_2(MeCN)_2$	$Ti(OPr^i)_4$	0
16	**1a**	$PdCl_2(MeCN)_2$-PPh_3	$Ti(OPr^i)_4$	92
17	**1a**	$Pd(OCOCF_3)_2$-PPh_3	$Ti(OPr^i)_4$	94
18	**1a**	$PdCl_2$-PPh_3	$Ti(OPr^i)_4$	23
19	**1a**	$Pd(acac)_2$-$(PhO)_3P$	$Ti(OPr^i)_4$	44
20	**1a**	$Pd(acac)_2$-Bu_3P	$Ti(OPr^i)_4$	33
21	**1a**	$Pd(acac)_2$-$(2\text{-}MePh)_3P$	$Ti(OPr^i)_4$	16
22	**1a**	$Pd(acac)_2$-$(2\text{-}furyl)_3P$	$Ti(OPr^i)_4$	98
23	**1a**	$Pd(acac)_2$-$(2\text{-}pyridyl)Ph_2P$	$Ti(OPr^i)_4$	91
24	**1a**	$Pd(acac)_2$-$(3\text{-}MePh)_3P$	$Ti(OPr^i)_4$	81
25	**1a**	$Pd(acac)_2$-$(4\text{-}MePh)_3P$	$Ti(OPr^i)_4$	98
26	**1a**	$Pd(acac)_2$-$(4\text{-}MeOPh)_3P$	$Ti(OPr^i)_4$	92
27	**1a**	$Pd(acac)_2$-$(4\text{-}FPh)_3P$	$Ti(OPr^i)_4$	69
28	**1a**	$Pd(acac)_2$-$(4\text{-}ClPh)_3P$	$Ti(OPr^i)_4$	18
29	**1a**	$Pd(acac)_2$-dppm	$Ti(OPr^i)_4$	21
30	**1a**	$Pd(acac)_2$-dppe	$Ti(OPr^i)_4$	31
31	**1a**	$Pd(acac)_2$-dppp	$Ti(OPr^i)_4$	92
32	**1a**	$Pd(acac)_2$-dppb	$Ti(OPr^i)_4$	93
33	**1a**	$Pd(OAc)_2$-(*R*)-BINAP[e]	$Ti(OPr^i)_4$	58[f]
34	**1a**	$Pd(OAc)_2$-(*S*,*S*)-DIOP[g]	$Ti(OPr^i)_4$	63[h]
35	**1b**	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	92
36	**1c**	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	70

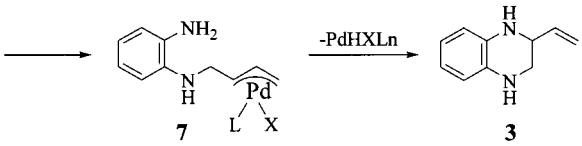
[a] Reaction conditions: **1** (1 mmol), **2** (0.8 mmol), Pd catalyst (0.01 mmol), ligand (0.04 mmol), titanium reagent (0.25 mmol), and molecular sieves 4 Å (200 mg) in benzene (5 mL) were refluxed for 3 h. [b] Isolated yield. [c] Stirred at 50 °C for 12 h. [d] 0.1 mmol of $Ti(OPr^i)_4$ was used. [e] (*R*)-2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl. [f] ee (%) (config): 19 (*S*). [g] (2*S*,3*S*)-2,3-*O*-Isopropylidene-2,3dihydroxy-1,4-bis(diphenylphosphanyl)butane. [h] ee (%) (config): 9 (*S*).

Scheme 2



Scheme 3





Intermolecular nucleophilic substitution of the amino group of **1** takes place at the less hindered terminus of the π-allyl system to give the allylic amine **6**. Intramolecular nucleophilic attack on the second π-allylpalladium intermediate **7** at the more substituted internal allylic carbon atom produces **3**.

Conclusions

In summary, we have prepared 1,2,3,4-tetrahydro-2-vinylquinoxalines in good yields in the presence of a palladium catalyst. This cyclization proceeds through tandem allylic substitution reaction between *o*-phenylenediamines and 2-butene-1,4-diol via π-allylpalladium intermediates.

(14) $Ti(OPr^i)_4$ may accelerate the reduction of $Pd(OAc)_2$ to Pd(0) species: Satoh, T.; Itoh, K.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2121.

Experimental Section

General Considerations. General Method. All reactions were carried out under a nitrogen atmosphere. Solvents were dried and distilled by known methods. Column chromatography was performed on silica gel. All melting points were uncorrected. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer. Proton and carbon-13 NMR were measured with a Unity-400 spectrometer. Carbon multiplicities were obtained from DEPT experiments. Chemical shifts (δ) and coupling constants (Hz) were measured with respect to TMS or chloroform-d_1. MS and high-resolution mass spectra (HRMS) were taken on a Hewlett-Packard 5989A or JEOL JMS D-100 instrument, with a direct

inlet system. Optical rotations were determined using a Jasco P-1020 polarimeter. Analytical HPLC was performed using a Shimadzu instrument with a photodiode array detector. All the following chemicals were commercially available and used without further purification. $Pd(OCOCF_3)_2$, 1,3-bis(diphenylphosphino)propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb), (2-pyridyl)Ph_2P, (3-MePh)$_3P$, (4-MePh)$_3P$, and (2*S*,3*S*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane [(*S*,*S*)-DIOP] were purchased from Aldrich. $Pd(OAc)_2$, $PdCl_2$, MS 4Å, PPh_3, $(PhO)_3P$, and pyridine were purchased from Riedel-de Haen. $Pd(acac)_2$ (acac = acetylacetonate), 1,1-bis(diphenylphosphino)methane (dppm), (2-MePh)$_3P$, (2-furyl)$_3P$, (4-MeOPh)$_3P$, (4-ClPh)$_3P$, and (4-FPh)$_3P$ were purchased from Lancaster. *o*-Phenylenediamine was purchased from Acros Organics. 4,5-Dimethyl-1,2-phenylenediamine, 4,5-dichloro-1,2-phenylenediamine, 2-butene-1,4-diol, $Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, 1,2-bis(diphenylphosphino)ethane (dppe), Bu_3P, (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl [(*R*)-BINAP], and titanium reagents were purchased from TCI.

General Procedure for the Palladium-Catalyzed Reaction of 2-Butene-1,4-diol. Reaction with *o*-Phenylenediamine (1a). A mixture of *o*-phenylenediamine (**1a**) (108 mg, 1 mmol), 2-butene-1,4-diol (**2**) (70 mg, 0.8 mmol), $Pd(acac)_2$ (3 mg, 0.01 mmol), PPh_3 (10.5 mg, 0.04 mmol), $Ti(OPr^i)_4$ (0.075 mL, 0.25 mmol), and MS 4Å (200 mg) in benzene (5 mL) was refluxed under nitrogen for 3 h. After cooling, the reaction mixture was filtered through Celite and the solvent was distilled under reduced pressure. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to give 152 mg (95%) of the cyclized product **3a**.

1,2,3,4-Tetrahydro-2-vinylquinoxaline (3a).[9] IR (KBr): ν 3367 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (dd, J = 7.6, 10.8 Hz, 1H, CH), 3.37 (dd, J = 3.2, 10.8 Hz, 1H, CH), 3.57 (bs, 2H, NH × 2), 3.85 (dtt, J = 1.2, 3.2, 7.2 Hz, 1H, CH), 5.14 (ddd J = 1.2, 1.6, 10.4 Hz, 1H, vinyl H), 5.26 (ddd J = 1.2, 1.6, 17.2 Hz, 1H, vinyl H), 5.83 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H, vinyl H), 6.44−6.48 (m, 2H, ArH), 6.54−6.58 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.44 (CH_2), 52.97 (CH), 114.49 (CH), 114.64 (CH), 116.37 (CH_2), 118.71 (CH), 118.95 (CH), 132.87 (C), 133.14 (C), 137.99 (CH). EI-MS: *m*/*z* 160 (M^+), 145, 133, 119, 104, 92, 77. EI-HRMS calcd for $C_{10}H_{12}N_2$: 160.1001. Found: 160.1002.

1,2,3,4-Tetrahydro-6,7-dimethyl-2-vinylquinoxaline (3b). Mp: 87−88 °C. IR (KBr): ν 3410 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6H, CH_3 × 2), 3.11 (dd, J = 7.6, 10.4 Hz, 1H, CH), 3.31 (bs, 2H, NH × 2), 3.32 (dd, J = 2.8, 10.8 Hz, 1H, CH), 3.87 (dtt, J = 1.2, 3.2, 7.6 Hz, 1H, CH), 5.15 (ddd, J = 1.2, 1.6, 10.4 Hz, 1H, vinyl H), 5.28 (ddd, J = 1.2, 1.6, 17.2 Hz, 1H, vinyl H), 5.87 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H, vinyl H), 6.32 (s, 1H, ArH), 6.33 (s, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.84 (CH_3), 18.87 (CH_3), 46.84 (CH_2), 53.30 (CH), 116.22 (CH_2), 116.36 (CH), 116.71 (CH), 126.54 (C), 127.04 (C), 130.47 (C), 131.06 (C), 138.18 (CH). EI-MS: *m*/*z* 188 (M^+), 172, 161, 147, 131, 120, 103, 91, 77. EI-HRMS calcd for $C_{12}H_{16}N_2$: 188.1313. Found: 188.1310.

6,7-Dichloro-1,2,3,4-tetrahydro-2-vinylquinoxaline (3c). Mp: 66.5−68 °C. IR (KBr): ν 3424 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (dd, J = 7.2, 11.2 Hz, 1H, CH), 3.33 (dd, J = 3.2, 11.2 Hz, 1H, CH), 3.66 (bs, 2H, NH × 2), 3.85 (dtt, J = 1.2, 3.2, 7.2 Hz, 1H, CH), 5.19 (ddd, J = 1.2, 1.2, 10.4 Hz, 1H, vinyl H), 5.30 (ddd, J = 1.2, 1.2, 17.2 Hz, 1H, vinyl H), 5.81 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H, vinyl H), 6.49 (s, 1H, ArH), 6.51 (s, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.78 (CH_2), 52.44 (CH), 114.76 (CH), 114.80 (CH), 117.04 (CH_2), 120.38 (C), 120.52 (C), 132.59 (C), 132.74 (C), 137.14 (CH). EI-MS: *m*/*z* 232 (M^+ + 4), 230 (M^+ + 2), 228 (M^+), 203, 201, 187, 166, 152, 133, 109, 101, 76. EI-HRMS calcd for $C_{10}H_{10}Cl_2N_2$: 228.0221. Found: 228.0220.

Determination of the Configuration of Compound 3a. The enantiomeric excess of 1,2,3,4-tetrahydro-2-vinylquinoxaline (**3a**) was determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H, eluent; *n*-hexane/2-propanol, 80:20), with the enantiomer *R* being eluted first. A solution of **3a** (80 mg, 0.5 mmol), exhibiting $[\alpha]_D^{20}$ +4.6 (*c* 3.73, $CHCl_3$), tosyl chloride (477 mg, 2.5 mmol), and pyridine (237 mg, 3 mmol) was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was hydrolyzed with water (2 mL) and extracted with CH_2Cl_2. Evaporation of the solvent gave 1,2,3,4-tetrahydro-1,4-bis(*p*-tolylsulfonyl)-2-vinylquinoxaline (**4**)[9] having $[\alpha]_D^{20}$ +9.3 (*c* 4.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 6H, CH_3 × 2), 3.29 (dd, J = 4.4, 12.8 Hz, 1H, CH), 4.04 (dd, J = 4.4, 12.8 Hz, 1H, CH), 5.04 (tq, J = 2.0, 4.4 Hz, 1H, CH), 5.12 (dd, J = 1.6, 10.4 Hz, 1H, vinyl H), 5.28 (dd, J = 1.6, 17.2 Hz, 1H, vinyl H), 5.62 (ddd, J = 4.8, 10.4, 17.2 Hz, 1H, vinyl H), 7.00−7.07 (m, 2H ArH), 7.22 (t, J = 8.8 Hz, 3H, ArH), 7.26 (s, 1H, ArH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.52−7.57 (m, 3H, ArH), 7.74−7.78 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.56 (CH_3), 21.62 (CH_3), 47.95 (CH_2), 55.77 (CH), 118.79 (CH_2), 119.53 (CH), 123.75 (CH), 125.67 (CH), 126.04 (C), 126.10 (CH), 127.05 (CH), 127.28 (CH), 129.77 (CH), 129.88 (CH), 130.67 (C), 133.41 (CH), 135.69 (C), 136.43 (C), 144.18 (C), 144.21(C).

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