JOC The Journal of Organic Chemistry

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Scalable Synthesis of Highly Reactive 1,3-Diamino Dienes from Vinamidinium Salts and Their Use in Diels–Alder Reactions

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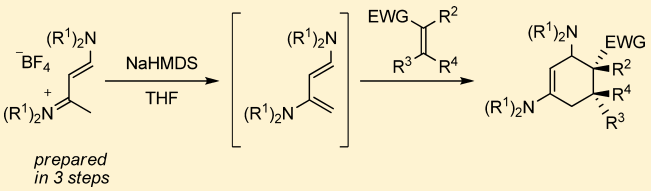
Supporting Information

ABSTRACT: A practical and chromatography-free synthesis of vinamidinium salts and their use as diene precursors in Diels–Alder reactions is reported. Additionally, 1,3-dipyrrolidino-1,3-butadiene was shown to be significantly more reactive than Rawal's diene in a competition experiment.



The Diels–Alder reaction[1] is one of the most widely used transformations for the synthesis of carbocycles due in part to its wide applicability in natural product synthesis.[2] It has been well established that the reactivity of the diene is increased and the regioselectivity is enhanced in normal electron-demand Diels–Alder reactions when electron-donating groups are introduced at positions 1 and 3.[3] Among dienes displaying this substitution pattern, 3-silyloxy dienes have found widespread use in synthesis and are exemplified by 1-alkoxy- (**1**),[4] 1-(dialkylamino)- (**2**),[5] and 1-(alkylthio)- (**3**),[6] 3-(trialkylsilyloxy)-1,3-butadienes (Figure 1).

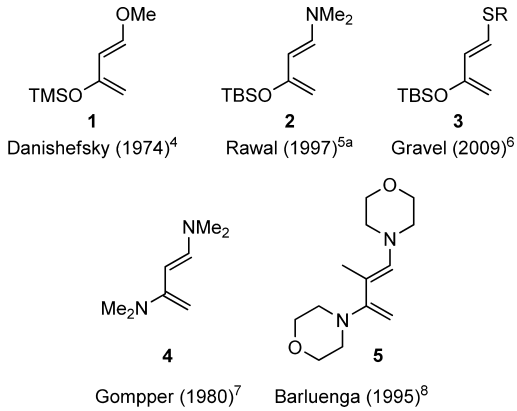
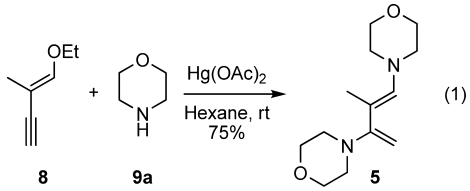


Figure 1. Representative silyloxy dienes and diamino dienes.

In 1974, Danishefsky and Kitahara introduced 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**1**) as a highly reactive functionalized diene.[4] Two decades later, Rawal and co-workers found that replacing the methoxy substituent in **1** with an *N*,*N*-dimethylamino group (**2**) increases the reactivity >3000 times.[5b] More recently, our research group developed 1-(alkylthio)-3-(silyloxy)-1,3-butadienes (**3**), which were found to be slightly less reactive than **1**.[6] Despite the usefulness of dienes **1**–**3**, these reagents have limited hydrolytic stability and they are generally prepared immediately prior to use. In addition, the noncatalyzed Diels–Alder reactions of these dienes with synthetically useful but moderately reactive dienophiles can be slow. For instance, the reaction between Rawal's diene (**2**) and α-substituted cyclohexenones requires prolonged heating in toluene, and to the best of our knowledge, no reaction has been reported with α,β-unsaturated amides.

With the aim of expanding the scope of available dienophiles in Diels–Alder reactions, we became interested in investigating the reactivity of 1,3-diamino-1,3-butadienes. Surprisingly, few studies have been reported on these potentially useful and highly reactive dienes as substrates in Diels–Alder reactions. In 1980, Gompper and co-workers reported the in situ preparation of 1,3-bis(dimethylamino)-1,3-butadiene (**4**) from the corresponding vinamidinium salt and its subsequent Diels–Alder reaction with dimethyl acetylenedicarboxylate to access a polysubstituted aromatic ring in modest yield (43%).[7] Other vinamidinium salts bearing additional functional groups were shown to behave similarly with this dienophile. In 1995, Barluenga and co-workers reported the synthesis of 1,3-dimorpholino-2-methyl-1,3-butadiene (**5**) and its reactions with various dienophiles (eq 1).[8] However, the method used to prepare this



diamino diene is not generally applicable to a wide variety of diamino dienes and requires the use of toxic mercury salts. Moreover, we have found 1,3-diamino-1,3-butadienes (including **5**) to be difficult to handle and purify due to their high susceptibility toward hydrolysis.

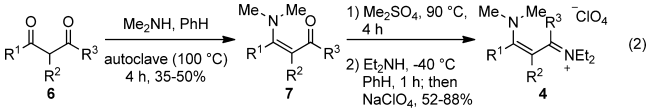
We thus set out to develop a practical and general method to access vinamidinium salts that would allow us to systematically assess the reactivity of 1,3-diamino-1,3-butadienes in Diels–Alder

Received: December 22, 2011
Published: March 7, 2012

   dx.doi.org/10.1021/jo202655h | *J. Org. Chem.* 2012, 77, 3576–3582

reactions. In addition, we were interested in examining the difference in reactivity between these dienes and Rawal's diene (**2**).

To access different vinamidinium salts, we required a robust and efficient method for their preparation. Arnold and coworkers[9] reported a preparation of vinamidinium salts which consisted in the treatment of 1,3-dicarbonyl compounds (**6**) with a solution of dimethylamine in benzene and heating in an autoclave to furnish vinylogous amides (**7**) (eq 2). These were



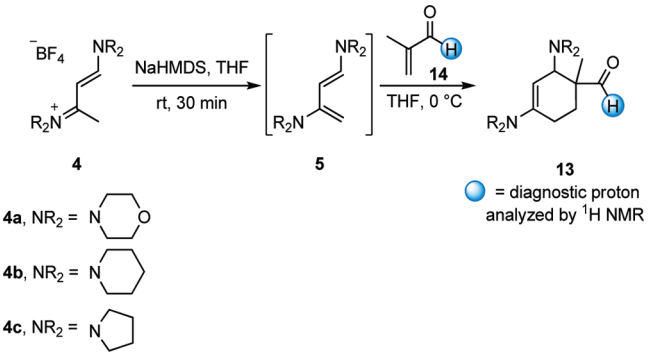
then *O*-alkylated with dimethylsulfate followed by treatment with a secondary amine to afford vinamidinium salts **4**. We opted to follow this general route with some modifications that would increase the practicality and overall yield toward 1-methyl-1,3-vinamidinium salts.

Employing the straightforward preparation of vinylogous amides reported by Rawal and Kozmin,[5a] 4-methoxy-3-buten-2-one (**10**) was mixed with the corresponding amines (**9**) in dichloromethane to cleanly afford vinylogous amides (**11**) in excellent yields. Subsequent alkylation of **11** using Meerwein's reagent[10] produced iminium salts **12** in moderate yields following recrystallization. Finally, vinamidinium salts **4** were cleanly obtained on a gram scale[11] via an addition–elimination process of secondary amines **9** onto iminium salts **12** (Scheme 1).[12] Whereas **4a–c** could be easily recrystallized using a dichloromethane/ethyl acetate system, the much less crystalline **4d,e** could not be conveniently purified and were not considered for further study.

With vinamidinium salts **4a–c** in hand, their conversion to the corresponding diamino dienes was then explored. Among the various bases (LiH, NaH, DBU, KHMDS, NaHMDS) and solvents (CH_2Cl_2, THF) tested, conditions utilizing NaHMDS in THF were found to cleanly and rapidly generate the desired dienes in solution. Whereas dienes **5a** and **5b** could be isolated following concentration in vacuo, 1,3-dipyrrolidino-1,3-butadiene (**5c**) proved to be very sensitive to moisture and decomposed rapidly when exposed to air. Attempts to purify dienes **5a** and **5b** via bulb-to-bulb distillation led to decomposition above 120 °C. In light of the convenience in handling stable, crystalline vinamidinium salts **4a–c**, their use as in situ precursors to diamino dienes was explored next.

The relative reactivity of dienes **5a–c** in Diels–Alder reactions was assessed with methacrolein (**14**) as the dienophile partner (Table 1). A marked difference in reactivity can be observed among diamino dienes **5a–c**. When aliquots of the

Table 1. Comparison of Diamino Dienes 5a–c in the Diels–Alder Reaction with Methacrolein



entry	diene	conversion[a] (%) (5 min)	conversion[a] (%) (30 min)
1	**5a**	5	25
2	**5b**	22	52
3	**5c**	51	>95

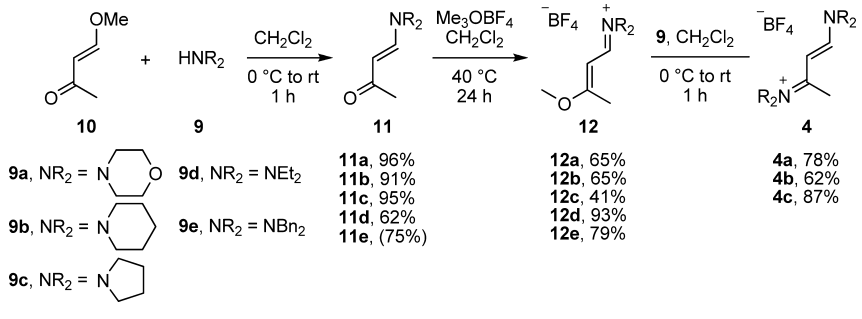
[a]Percent conversion was determined from ^{1}H NMR analysis of the crude reaction mixture by comparing diagnostic peaks between **13** and **14**

reaction were taken after 5 min, cycloadditions with 1,3-dimorpholino-1,3-butadiene (entry 1) and 1,3-dipiperidino-1,3-butadiene (entry 2) were much slower than that with 1,3-dipyrrolidino-1,3-butadiene (entry 3). After 30 min, the reactions with **5a** and **5b** showed only 25 and 52% conversion, respectively, whereas diamino diene **5c** was cleanly and nearly completely converted into the desired product.

Based on the comparative study of vinamidinium salts, **5c** was identified as the most reactive diene and its reactions with a variety of dienophiles were investigated (Table 2).

Although the cycloaddition with methacrolein (**14**) could be performed cleanly at room temperature as determined by ^{1}H NMR spectroscopy, attempts to hydrolyze cycloadduct **13a** were accompanied with significant decomposition. Therefore, the reaction mixture containing the cycloadduct was treated with $LiAlH_4$ to afford the corresponding alcohol (**20**) in good yield following an acidic aqueous workup (entry 1). Surprisingly, when the mixture of the reaction between **5c** and acrolein (**15**) was concentrated and purified by flash column chromatography, dienamine **21** was obtained in excellent yield instead of the expected enone (entry 2). This product is a cyclic congener of Zincke's aldehydes[13] (5-(dialkylamino)-2,4-pentadienal) which have recently received increased attention as building blocks for alkaloid natural product synthesis.[14] The synthesis of dienamine **21** was also performed on a gram scale with similar efficiency (88% yield), thereby establishing the viability of diene **5c** in

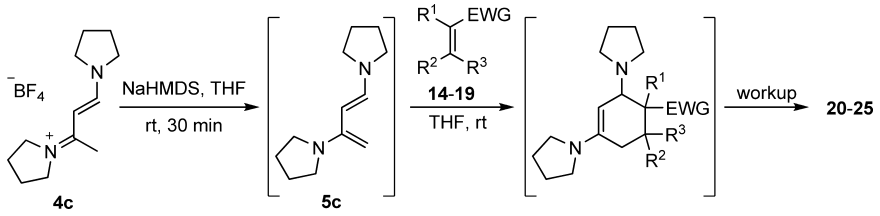
Scheme 1. Three-Step Sequence for the Synthesis of Vinamidinium Salts 4a–c[a]

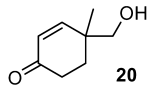
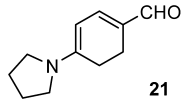
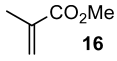
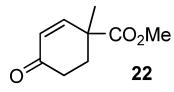
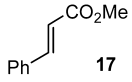
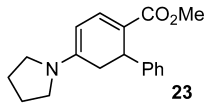
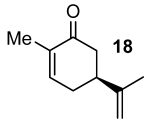
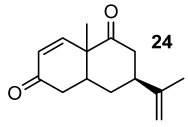
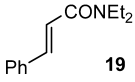
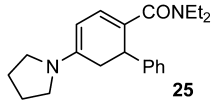


[a]Numbers in parentheses represent percent conversion. Compounds **12d–e** were obtained in ca. 70% purity as determined by ^{1}H NMR analysis.

dx.doi.org/10.1021/jo202655h | J. Org. Chem. 2012, 77, 3576–3582

Table 2. Diels-Alder Reactions with in Situ Generated 1,3-Dipyrrolidino-1,3-butadiene (5c)



entry	dienophile	time (h)	workup	product	yield (%)[a]
1	 14	0.5	$LiAlH_4/H_3O^+$	 20	71
2	 15	1	Concentration/FCC [b]	 21	93
3	 16	1	Concentration/FCC [b]	 22	87
4	 17	4	Filtration through Celite®	 23	87
5	 18	12	Concentration/FCC [b]	 24	67 [c]
6[d]	 19	20	Concentration	 25	(84)

[a]Yields of pure isolated products; number in parentheses represents the percent conversion. [b]FCC = flash column chromatography. [c]Obtained as a 2:1 mixture of diastereomers. [d]The reaction mixture was heated at 65 °C for 20 h.

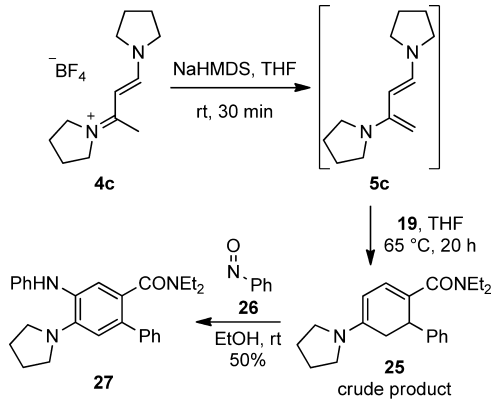
multistep synthetic endeavors. The reaction between methyl methacrylate (**16**) and diene **5c** rapidly furnished the cycloadduct (entry 3). In this case, hydrolysis to the corresponding enone **22** proceeded uneventfully. As was the case with acrolein, the presence of an α proton in methyl cinnamate (**17**) led to dehydroamination of the cycloadduct to generate dienamine **23** in good yield (entry 4). Although dienamine **23** was not tolerant of acidic workup, it could be efficiently isolated from the crude mixture by recrystallization. The use of the sterically hindered (+)-carvone (**18**) led to a slower cycloaddition at room temperature. Indeed, 12 h was required to furnish the desired hydrolyzed cycloadduct **24** in moderate yield and poor diastereoselectivity (2:1 dr) (entry 5). Nevertheless, this result stands in stark contrast to the reaction employing Rawal's diene **2a**, which required heating at 110 °C for 48 h and afforded **24** as a 1:1 mixture of diastereomers.[5c] These observations are indicative of a much greater reactivity for diene **5c** compared to diene **2a** (vide infra).

In view of the high reactivity of diene **5c**, we decided to investigate its [4 + 2] cycloaddition with the poorly electrophilic amide **19**. Initial attempts at performing the cycloaddition reaction at room temperature over extended periods (>20 h) resulted in incomplete conversion along with diene decomposition products. Suspecting that decomposition was initiated by hydrolysis brought about by adventitious water, the reaction mixture was heated at 65 °C for 20 h. As expected, the desired cycloadduct was successfully obtained while decomposition remained minimal over the shorter reaction time. Although dehydroaminated cycloadduct **25** was too unstable to purify, it could be used productively in a subsequent transformation. Inspired by a previously reported synthesis of polysubstituted anilines by Ramachary and co-workers,[15] crude product **25** was subjected to an amination/isoaromatization sequence in the presence of nitrosobenzene (**26**). The resulting *N,N*-diethylbiphenyl carboxamide derivative **27** was obtained in good overall yield over two steps (Scheme 2).

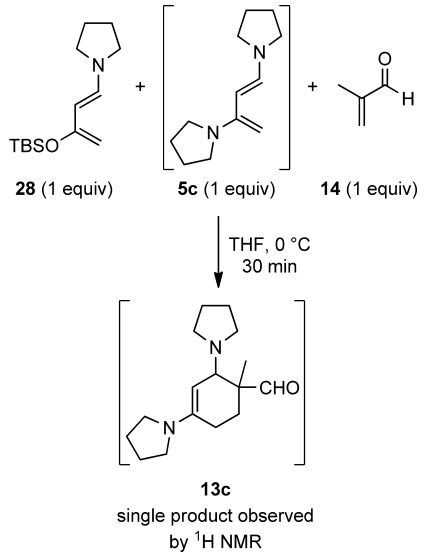
As a result of the exceptional reactivity of diamino diene **5c**, we decided to compare it to Rawal's pyrrolidine-substituted diene **28** in a competition reaction using methacrolein (**14**) as the dienophile (Scheme 3).[16] In the event, diene **5c** proved to be much more reactive based on the fact that **13c** was the only cycloadduct present in the reaction mixture along with diene **28**. Assuming up to 5% of the cycloadduct formed from Rawal's diene **28** and methacrolein could be present without detection

dx.doi.org/10.1021/jo202655h | J. Org. Chem. 2012, 77, 3576–3582

Scheme 2. Two-Step Synthesis of Trisubstituted Biphenyl 27



Scheme 3. Competition Reaction between Diamino Diene 5c and Rawal's Diene 28



by ^{1}H NMR analysis, diamino diene **5c** would be at least 20 times more reactive that **28**. Based on the reaction conditions used in the cycloadditions between diene **5c** and dienophiles **18** and **19**, we suspect the difference in reactivity is in fact much larger.

In conclusion, we have reported a facile and scalable synthesis of vinamidinium salts (**4**) in good overall yield. The reactivity of three vinamidinium salt-derived diamino dienes was investigated. The highly reactive nature of 1,3-dipyrrolidino-1,3-butadiene (**5c**) allowed Diels–Alder reactions to proceed with a wide range of dienophiles including the poorly reactive *N*,*N*-diethylcinnamamide (**19**). In addition, the use of dienophiles lacking an α substituent led to an efficient synthesis of 1-amino-cyclohexa-1,3-diene derivatives (**21**, **23**, and **25**). Finally, diamino diene **5c** was shown to be at least 20 times more reactive than Rawal's diene **28** in its cycloaddition with methacrolein. We expect the high reactivity of 1,3-dipyrrolidino-1,3-butadienes to find useful applications in synthesis.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed under inert atmosphere employing oven-dried Schlenk tubes. Anhydrous solvents were dried using a solvent purification system and stored under nitrogen over predried 3 Å molecular sieves. Molecular sieves were dried by heating in a heating mantle at 300 °C (temperature measured with a thermocouple) under high vacuum (0.5 mmHg) for 24 h. Silica gel SI 60 (40–63 μm) was used for column chromatography. NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The residual solvent protons (^{1}H) ($CHCl_3$ 7.26 δH) or the solvent carbons (^{13}C) ($CHCl_3$ 77.23 δC) were used as internal standards for chemical shifts. High-resolution mass spectrometry (HRMS) was performed on a double-focusing high-resolution spectrometer. EI ionization was accomplished at 70 eV. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. All samples were prepared as a film on a KBr disk or KBr pellet using IR grade potassium bromide. Melting points were measured in an electrothermal digital melting point apparatus and are uncorrected. Dienophiles **14**–**18** were purchased from commercial sources and were used without further purification. Dienophile **19** was prepared following a reported procedure from the literature.[17] Compound **10** is commercially available and was purified via bulb-to-bulb distillation prior to use. Amines **9a**-**e** were freshly distilled from potassium hydroxide (pellets) prior to use.

General Procedure for the Preparation of Vinylogous Amides 11a–c. To a solution of (3*E*)-4-methoxy-3-buten-2-one (20 mmol, 1 equiv) in dry dichloromethane (20 mL) was slowly added a secondary amine (24 mmol, 1.2 equiv) at 0 °C, the reaction mixture was stirred at room temperature for 1 h, and then the solvent was evaporated in vacuo to obtain a crude yellow oil which was purified by filtration through a plug of silica gel rinsing with ethyl acetate followed by evaporation of the solvent to afford essentially pure vinylogous amide.

*(3E)-4-Morpholinyl-3-buten-2-one (**11a**).* The reaction was performed as described in the general procedure; 2.92 g (96%) of product as light yellow oil: FTIR (KBr film) ν_{max} (cm^{-1}) 2965, 2900, 2854, 1659, 1610, 1567, 1446, 1368, 1114, 1025, 960, 635; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 13.0 Hz, 1H), 5.14 (d, J = 13.0 Hz, 1H), 3.67–3.63 (m, 4H), 3.23–3.22 (m, 4H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 151.1, 97.2, 68.0, 66.1, 66.1, 46.4, 28.1; HRMS (EI$^+$) m/z calcd for $C_8H_{13}NO_2$ [M]$^+$ 155.0946, found 155.0945.

*(3E)-4-Piperidinyl-3-buten-2-one (**11b**).* The reaction was performed as described in the general procedure; 2.69 g (91%) of product as light yellow oil: FTIR (KBr film) ν_{max} (cm^{-1}) 2937, 2855, 1658, 1606, 1566, 1447, 1366, 1236, 1114, 957; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 13.0 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 3.23 (brs, 4H), 2.07 (s, 3H), 1.65–1.58 (m, 6H); HRMS (EI$^+$) m/z calcd for $C_9H_{15}NO$[M]$^+$ 153.1154, found 153.1157. All spectroscopic data match those reported by Yus and co-workers.[18]

*(3E)-4-Pyrrolidinyl-3-buten-2-one (**11c**).* The reaction was performed as described in the general procedure; 2.63 g (95%) of product as light yellow oil: ^{1}H NMR(500 MHz, $CDCl_3$) δ 7.68 (d, J = 12.8 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 3.47–3.14 (m, 4H), 2.10 (s, 3H), 1.98–1.92 (m, 4H). The spectroscopic data match with that reported by Rawal and co-workers.[5c]

General Procedure for the Preparation of 3-Methoxybut-2-enylidene-4-iminium Salts 12a–c. To a solution of trimethyloxonium tetrafluoroborate (1.77 g, 12.0 mmol, 1 equiv) in dichloromethane (15 mL) was added vinylogous amide **11** (15.0 mmol, 1.25 equiv). The reaction mixture was refluxed for 24 h and then concentrated in vacuo to give the crude product, which was purified by recrystallization from dichloromethane and ethyl acetate.

*(Z)-1-(3-Methoxybut-2-enylidene)morpholinium Tetrafluoroborate (**12a**).* The reaction was performed as described in the general procedure; 2.05 g (65%) of light orange crystals were obtained after recrystallization: mp 135–136 °C; FTIR (KBr pellet) ν_{max} (cm^{-1}) 2865, 1637, 1581, 1464, 1390, 1240, 1053, 823, 646, 592, 521; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.73 (d, J = 11.4 Hz, 1H), 6.19 (d, J = 11.4 Hz, 1H), 4.05–4.03 (m, 7H), 3.93 (m, 2H), 3.87 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 187.7, 165.8, 94.8, 67.9, 67.0, 59.2, 58.3, 50.3, 19.3; HRMS (ESI/TOF$^+$) m/z calcd for $C_9H_{16}NO_2$ [M]$^+$ 170.1175, found 170.1174.

*(Z)-1-(3-Methoxybut-2-enylidene)piperidinium Tetrafluoroborate (**12b**).* The reaction was performed as described in the general procedure; 1.99 g (65%) of light yellow crystals was obtained after recrystallization: mp 121–122 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 2941,

dx.doi.org/10.1021/jo202655h | J. Org. Chem. 2012, 77, 3576–3582

1636, 1587, 1473, 1305, 1244, 1084, 847, 882, 617, 533, 521; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 11.5 Hz, 1H), 5.84 (d, J = 11.5 Hz, 1H), 3.97(s, 3H), 3.90 (dd, J = 5.7, 5.5 Hz, 2H), 3.80 (dd, J = 5.9, 5.1 Hz, 2H), 2.37 (s, 3H), 1.92−1.78 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 163.3, 93.2, 59.1, 58.0, 49.8, 26.8, 25.8, 23.1, 18.9; HRMS (ESI/TOF$^+$) m/z calcd for $C_{10}H_{18}NO[M]^+$ 168.1382, found 168.1389.

*(Z)-1-(3-Methoxybut-2-enylidene)pyrrolidinium Tetrafluoroborate (**12c**).* The reaction was performed as described in the general procedure; 1.19 g (41%) of white crystals was obtained after recrystallization: mp 121−123 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 2948, 2085, 1635, 1590, 1433, 1394, 1300, 1268, 1240, 1058, 837, 618, 586, 533, 521 ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 11.4 Hz, 1H), 5.61 (d, J = 11.4 Hz, 1H), 4.06 (t, J = 6.9 Hz, 2H), 3.96 (s, 3H), 3.76 (t, J = 7.0 Hz, 2H), 2.36 (s, 3 H), 2.17 (quint, J = 7.0 Hz, 2H), 2.08 (quint, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 162.2, 95.1, 58.3, 56.4, 50.4, 24.8, 24.8, 19.0; HRMS (ESI/TOF$^+$) m/z calcd for $C_9H_{16}NO[M]^+$ 154.1226, found 154.1225.

General Procedure for the Preparation of Vinamidinium Salts 4a−c. To a solution of iminium salt **12** (5 mmol, 1 equiv) in dichloromethane (5 mL, 1 M) was added a secondary amine (6 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the crude solid was purified by recrystallization from dichloromethane and ethyl acetate.

*(Z)-1-(3-(Morpholinyl)but-2-enylidene)morpholinium Tetrafluoroborate (**4a**).* The reaction was performed as described in the general procedure; 1.22 g (78%) of light orange crystals was obtained after recrystallization: mp 143−145 °C; FTIR (KBr pellet) ν_{max} (cm^{-1}) 3440, 2924, 2860, 1613, 1562, 1486, 1413, 1387, 1347, 1292, 1233, 929, 862, 820, 639, 621, 533, 521, 467; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.22 (d, J = 12.2 Hz, 1H), 5.86 (d, J = 12.2 Hz, 1H), 3.87−3.74 (m, 16H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.9, 160.0, 91.3, 68.0, 66.8, 56.0, 47.9, 16.5; HRMS (EI$^+$) m/z calcd for $C_{12}H_{21}N_2O_2$ $[M]^+$ 225.1597, found 225.1598.

*(Z)-1-(3-(Piperidinyl)but-2-enylidene)piperidinium Tetrafluoroborate (**4b**).* The reaction was performed as described in the general procedure; 0.95 g (62%) of off white crystals was obtained after recrystallization: mp 111−112 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 3403, 2934, 2856, 1614, 1560, 1480, 1413, 1386, 1358, 1272, 1238, 1054, 854, 815, 771, 617, 533, 521; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 12.2 Hz, 1H), 5.42 (d, J = 12.2 Hz, 1H), 3.65 (m, 6H), 3.51 (m, 2H), 2.33 (s, 3H), 1.74−1.71 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 158.3, 89.6, 57.1, 47.5, 26.8, 25.5, 23.9, 23.8, 16.5; HRMS (EI$^+$) m/z calcd for $C_{14}H_{25}N_2$ $[M]^+$ 221.2012, found 221.2016.

*(Z)-1-(3-(Pyrrolidinyl)but-2-enylidene)pyrrolidinium Tetrafluoroborate (**4c**).* The reaction was performed as described in the general procedure; 1.22 g (87%) of white crystals was obtained after recrystallization: mp 91−92 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 2970, 2871, 1917, 1569, 1450, 1408, 1353, 1329, 1300, 1271, 1229, 1072, 854, 792, 771, 618, 533, 521; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 12.1 Hz, 1H), 4.93 (d, J = 12.2 Hz, 1H), 3.82 (t, J = 6.8 Hz, 2H), 3.68 (t, J = 6.6 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 3.40 (t, J = 7.0 Hz, 2H), 2.36 (s, 3H), 2.12−2.05 (m, 6H), 1.99 (quint, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 154.4, 91.9, 53.9, 50.7, 50.1, 48.0, 24.9, 24.9, 24.8, 24.6, 17.0; HRMS (EI$^+$) m/z calcd for $C_{12}H_{21}N_2$ $[M]^+$ 193.1699, found 193.1689.

*Multigram Synthesis of **4c**.* To a solution of (3*E*)-4-methoxy-3-buten-2-one (1.68 g, 16.8 mmol, 1 equiv) in dry dichloromethane (18 mL) was slowly added pyrrolidine (1.68 mL, 20.2 mmol, 1.2 equiv) at 0 °C, the reaction mixture was stirred at room temperature for 1 h, and then the solvent was evaporated in vacuo to obtain a crude yellow oil (**11c**), which was added to a solution of trimethyloxonium tetrafluoroborate (1.75 g, 11.8 mmol, 0.7 equiv) in dichloromethane (15 mL). The reaction mixture was refluxed for 24 h and then concentrated in vacuo to give the crude product, which was purified by recrystallization from dichloromethane and ethyl acetate to obtain an orange crystalline solid. To a solution of the solid in dichloromethane (10 mL) was added pyrrolidine (1.68 mL, 20.2 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the crude solid was purified by recrystallization from dichloromethane and ethyl acetate, and 2.56 g (77%) of a light orange crystalline solid was obtained. This product was identical by ^{1}H NMR analysis to the one obtained on smaller scale above.

Diels−Alder Reactions with Vinamidinium Salt 4c. *Synthesis of 4-(Hydroxymethyl)-4-methylcyclohex-2-enone (**20**).* To a solution of vinamidinium salt **4c** (56 mg, 0.2 mmol, 1 equiv) in dry THF (1 mL, 0.2 M) was added NaHMDS (0.2 mL, 0.2 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. Methacrolein (**14**) (25 μL, 0.22 mmol, 1.1 equiv) was added, and stirring was continued for 30 min at room temperature. The reaction was cooled to −78 °C and treated with $LiAlH_4$ (0.4 mL, 0.4 mmol, 2 equiv, 1 M in Et_2O). The reaction mixture was stirred for 30 min at −78 °C and then warmed to room temperature. After being stirred for another 3 h, the resulting mixture was cooled to 0 °C and quenched by dropwise addition of water (0.1 mL), and the solids were removed by filtration. The residue was washed with Et_2O (3 × 5 mL), and the filtrate was dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was diluted in Et_2O (10 mL) and stirred overnight with saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4, the solvent was removed in vacuo, and the crude product was purified by flash column chromatography (70% ethyl acetate in hexanes) to give a light yellow oil in 71% yield (20 mg): ^{1}H NMR(500 MHz, $CDCl_3$) δ 6.73 (d, J = 10.1 Hz, 1H), 5.96 (d, J = 10.1 Hz, 1H), 3.57 (d, J = 10.7 Hz, 1H), 3.50 (d, J = 10.6 Hz, 1H), 2.50−2.46 (m, 2H), 2.22 (brs, 1H), 2.08 (ddd, J = 13.9, 8.8, 6.4 Hz, 1H), 1.75 (dt, J = 13.4, 6.4 Hz,1H), 1.14 (s, 3H). The spectroscopic data match those reported in the literature.[5c]

*Synthesis of 4-(Pyrrolidin-1-yl)cyclohexa-1,3-dienecarbaldehyde (**21**).* Small scale: To a solution of vinamidinium salt **4c** (112 mg, 0.4 mmol, 1 equiv) in dry THF (2 mL, 0.2 M) was added NaHMDS (0.4 mL, 0.4 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. Acrolein (**15**) (55 μL, 0.8 mmol, 2 equiv) was added, and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (100% ethyl acetate) to give a red solid in 93% yield (66 mg).

Gram scale: To a solution of vinamidinium salt **4c** (1.00 g, 3.6 mmol, 1 equiv) in dry THF (18 mL, 0.2 M) was added NaHMDS (3.6 mL, 3.6 mmol, 1 equiv, 1 M in THF) dropwise at 0 °C, and the reaction mixture was stirred for 30 min at room temperature. Acrolein (**15**) (0.48 mL, 7.2 mmol, 2 equiv) was added, and the reaction mixture was stirred for 30 min at room temperature. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (100% ethyl acetate) to give a red solid in 88% yield (554 mg): mp 91−92 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 2963, 2876, 2760, 2712, 1619, 1501, 1400, 1345, 1331, 1301, 1262, 1193, 1151, 1110, 651, 547, 253, 235, 234; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 6.91 (d, J = 7.0 Hz, 1H), 4.83 (d, J = 7.0 Hz, 1H), 3.43−3.30 (m, 4H), 2.57−2.46 (m, 4H), 1.96 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 157.2, 150.7, 122.0, 92.4, 48.2, 27.0, 25.3, 19.0; HRMS (EI$^+$) m/z calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154, found 177.1154.

*Synthesis of Methyl 1-Methyl-4-oxocyclohex-2-enecarboxylate (**22**).* To a solution of vinamidinium salt **4c** (112 mg, 0.4 mmol, 1 equiv) in dry THF (2 mL, 0.2 M) was added NaHMDS (0.4 mL, 0.4 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. Methyl methacrylate (**16**) (65 μL, 0.6 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to give a light yellow oil in 87% yield (59 mg): FTIR (KBr film) ν_{max} (cm^{-1}) 2955, 1733, 1684, 1457, 1262, 1114; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, J = 10.1 Hz, 1H), 5.91 (d, J = 10.1 Hz, 1H), 3.68 (s, 3H), 2.50−2.36 (m, 3H), 1.98−1.88 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 174.6, 151.7, 128.7, 52.6, 43.9, 34.6, 32.6, 24.9; HRMS (EI$^+$) m/z calcd for $C_9H_{12}O_3$ $[M]^+$ 168.0786, found 168.0788.

dx.doi.org/10.1021/jo202655h | J. Org. Chem. 2012, 77, 3576−3582

Synthesis of Methyl 6-Phenyl-4-(pyrrolidin-1-yl)cyclohexa-1,3-dienecarboxylate (23). To a solution of vinamidinium salt **4c** (56 mg, 0.2 mmol, 1 equiv) in dry THF (1 mL, 0.4 M) was added NaHMDS (0.2 mL, 0.2 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. A solution of methyl cinnamate (**17**) (33 mg, 0.2 mmol, 1.01 equiv) in THF (0.5 mL) was added, and the reaction mixture was stirred for 4 h at room temperature. The solids were removed by filtration through Celite and rinsed with ethyl acetate (6 × 10 mL). The filtrate was concentrated in vacuo, and the crude solid was purified by recrystallization from methanol and diethyl ether to give light yellow crystals in 87% yield (50 mg): mp 135−136 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 3338, 2945, 2867, 2361, 2336, 1680, 1524, 1479, 1459, 1430, 1362, 1343, 1305, 1300, 1086, 743, 699, 617, 533, 521; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.0 Hz, 1H), 7.31−7.29 (m, 2H), 7.24−7.22 (m, 2H), 7.17−7.14 (m, 1H), 4.70 (d, J = 7.0 Hz, 1H), 4.04 (dd, J = 9.6, 1.3 Hz, 1H), 3.63 (s, 3H), 3.25 (m, 4H), 2.98 (ddd, J = 16.3, 9.4, 1.3 Hz, 1H), 2.77 (dd, J = 16.5, 1.6 Hz, 1H), 1.90−1.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 151.5, 144.4, 140.3, 128.5, 127.6, 126.5, 111.8, 90.6, 51.1, 47.8, 37.2, 35.3, 25.3; HRMS (EI^+) m/z calcd for $C_{18}H_{21}NO_2$ $[M]^+$ 283.1572, found 283.1574.

Synthesis of (3R)-8a-Methyl-3-(prop-1-en-2-yl)-3,4,4a,5-tetrahydronaphthalene-1,6(2H,8aH)-dione (24). To a solution of vinamidinium salt **4c** (112 mg, 0.4 mmol, 1 equiv) in dry THF (2 mL, 0.2 M) was added NaHMDS (0.4 mL, 0.4 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. (+)-(*S*)-Carvone (**18**) (47 μL, 0.6 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to give a 2:1 mixture of diastereomers in 67% yield (58 mg): (major diastereomer) ^1H NMR(500 MHz, $CDCl_3$) δ 6.74 (d, J = 10.3 Hz, 1H), 6.05 (d, J = 10.3 Hz, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 2.69−2.62 (m, 2H), 2.51 (m, 1H), 2.42−2.36 (m, 3H), 2.13 (m, 1H), 1.77 (s, 3H), 1.73 (m, 1H), 1.47 (s, 3H); (minor diastereomer) ^1H NMR-(500 MHz, $CDCl_3$) δ 6.43 (dd, J = 10.1, 2.0 Hz, 1H), 6.05 (d, J = 10.1, 0.6 Hz, 1H), 4.77−4.76 (m, 1H), 4.69 (s, 1H), 2.85 (dd, J = 17.2, 5.1 Hz, 1H), 2.49 (m, 1H), 2.41−2.34 (m, 3H), 1.80 (m, 1H), 1.75 (m, 1H), 1.70 (s, 3H), 1.41 (s, 3H). The spectroscopic data match with that reported in the literature.5c

N,N-Diethyl-4-(phenylamino)-5-(pyrrolidin-1-yl)biphenyl-2-carboxamide (27). To a solution of vinamidinium salt **4c** (56 mg, 0.2 mmol, 1 equiv) in dry THF (0.5 mL, 0.4 M) was added NaHMDS (0.2 mL, 0.2 mmol, 1 equiv, 1 M in THF), and the reaction mixture was stirred for 30 min at room temperature. A solution of *N,N*-diethylcinnamamide (**19**) (41 mg, 0.2 mmol, 1 equiv) in THF (0.5 mL) was added. The stream of nitrogen was increased, and the septum on the Schlenk tube was replaced with a coldfinger. The reaction mixture was stirred and heated to reflux (65 °C) for 20 h. The mixture was cooled to ambient temperature, and transferred to a 50 mL round-bottom flask, and the solvent was removed in vacuo. The flask was then evacuated with nitrogen, and the crude product was dissolved in absolute ethanol (0.7 mL, 0.3 M). Molecular sieves (20 mg) and nitrosobenzene (**26**) (21 mg, 0.2 mmol, 1 equiv) were sequentially added to the flask. The mixture was stirred at room temperature for 3 h, filtered through a plug of basic alumina, and rinsed with THF. The volatiles were evaporated, and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to give a dark yellow solid in 50% yield (41 mg): R_f = 0.3; mp 170−171 °C; FTIR (KBr film) ν_{max} (cm^{-1}) 3302, 3050, 2970, 2872, 1597, 1556, 1498, 1346, 1274, 1099, 747, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45−7.49 (m, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.31−7.23 (m, 4H), 7.08 (d, J = 7.7 Hz, 2H), 7.00 (s, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.04 (brs, 1H), 3.71 (brs, 1H), 3.31−2.90 (m, 6H), 2.69 (brs, 1H), 1.92 (brs, 4H), 0.89 (t, J = 7.3 Hz, 3H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 143.4, 141.8, 140.6, 135.4, 131.7, 130.2, 129.6, 128.9, 128.4, 127.1, 120.7, 119.2, 117.8, 116.1, 51.3, 42.5, 38.4, 24.7, 13.6, 12.2; HRMS (EI^+) m/z calcd for $C_{27}H_{31}N_3O[M]^+$ 413.2467, found 413.2465.

Competition Experiment between Rawal's Diene (28) and Diamino Diene 5c. To a solution of vinamidinium salt **4c** (133 mg, 0.47 mmol, 1 equiv) in dry THF (1 mL) was added NaHMDS (0.47 mL, 0.47 mmol, 1 equiv, 1 M in THF), the reaction mixture was stirred for 30 min at room temperature followed by the addition of Rawal's diene (**28**) (120 mg, 0.47 mmol, 1 equiv) in dry THF (1.4 mL, final concentration 0.2 M) and cooled to 0 °C. Methacrolein (**14**) (40 μL, 0.47 mmol, 1 equiv) was added, and the mixture was stirred for 30 min at 0 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds and competition experiment. This material is free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant to M.G.), the Canada Foundation for Innovation, and the University of Saskatchewan for financial support.

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