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Palladium-catalyzed stereoselective synthesis of (*E*)-β,γ-unsaturated amides

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Abstract—A facile Suzuki type cross-coupling reaction of alkenylborane with 2-bromo-*N*,*N*-dimethylacetamide in the presence of a catalytic amount of tricyclohexylphosphine as the ligand has been demonstrated to be a convenient way for the synthesis of (*E*)-β,γ-unsaturated amides.

β,γ-Unsaturated amides are synthetically important key intermediates;[1] yet their synthesis is a tedious task. Nonetheless, a few methods for their preparation have been hitherto described. For example, the preparation of β,γ-unsaturated amides have involved palladium-catalyzed carbonylation of allylamines,[2] rhodium-catalyzed azacarbonylation of allyl phosphates,[3] ruthenium-catalyzed carbonylation of allylic alkyl carbonates,[4] conversion from allyl alcohol by the use of *N*,*N*-dimethylformamide acetals,[5] and cross-coupling reaction of alkenylborane with *N*,*N*-dialkyl(dimethylsulfuranylidene)acetamide.[6] In addition, Deng has reported[6] that (*E*)-β,γ-unsaturated amides could not be obtained from (*E*)-9-alkenyl-9-borabicyclo[3,3,1]nonane and α-bromoacetamide by Brown's procedure.[7] We have recently reported that the Suzuki type cross-coupling reaction of aryldioxaborolane and 2-bromo-*N*,*N*-dimethylacetamide could provide a convenient and simple way to the synthesis of α-arylacetamide in moderate to good yields.[8] Interestingly, we discovered that our Suzuki type cross-coupling conditions could be simply employed to the cross-coupling of alkenylboranes with 2-bromo-*N*,*N*-dimethylacetamide. Herein, we wish to report the results of preparing highly stereoselective α-alkenylacetamide from the stereodefined alkenylboranes, which can be easily obtained via hydroboration of terminal or internal acetylenes. Following is a representative procedure: To a mixture of $Pd(dba)_2$ (0.3 mmol), PCy_3 (0.6 mmol), K_3PO_4 (34 mmol) in 10 mL of dry THF was added 2-bromo-*N*,*N*-dimethylacetamide[9] (10 mmol) at 70°C. After stirring for 20 min, the alkenylborane prepared in situ in THF[10] was added and the mixture was stirred for another 16 h at 70°C. The mixture was quenched with water, extracted with EtOAc, and purified by column chromatography (hexane/EtOAc = 3/1). The (*E*)-configuration stereochemistry of target molecules were determined by means of either ^{1}H NMR or 2D NOESY spectral analysis.

The palladium-catalyzed cross-coupling reactions of various alkenylborane with 2-bromo-*N*,*N*-dimethylacetamide were studied and the results are summarized in Table 1. Alkenylborane obtained from hydroboration by using dicyclohexylborane is expected to give satisfied yields and no difficulty to isolate the desired products in the above Suzuki type cross-coupling reaction. However, the use of alkenylborane obtained from the commercial 9-BBN in THF gave the desired products in moderate yields, but it was found difficult to remove other unidentified by-products. On the other hand, the stereoselectivity of the carbon–carbon double bond could reach to 30:1 for (*E*)/(*Z*) by using 9-BBN and to 25:1 for (*E*)/(*Z*) by using dicyclohexylborane. 1-Alkyne with or without methoxyl group at propargyl position could give good results (entries 1, 2 and 3). The two vinylic protons of the β,γ-unsaturated products from 1-alkyne are accidentally equivalent in 400 MHz NMR spectrum. For comparison, we have run the 2D NOESY of the mixture of (*E*)- and (*Z*)-*N*,*N*-dimethyldec-3-enamide[11] and that of pure (*E*)-isomer. The (*Z*)-isomer does have cross peaks between the two

Keywords: Suzuki coupling reactions; alkenylborane; 2-bromo-*N*,*N*-dimethylacetamide.
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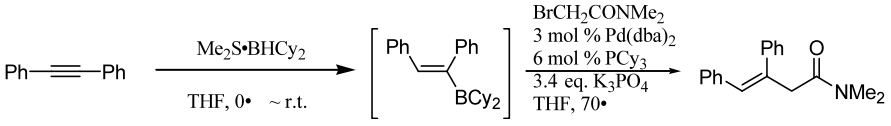
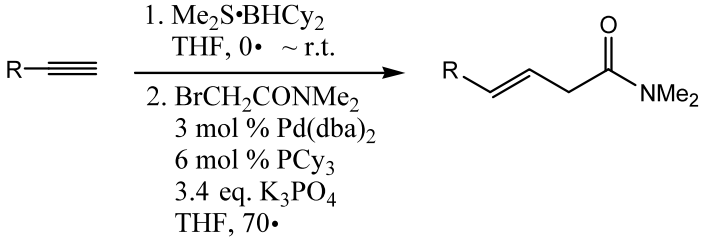
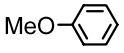
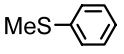
allylic protons at C-5 position (2.02 ppm) and the two protons at C-2 position (3.10 ppm), while there is no such corresponding cross peaks [the two allylic protons at C-5 position (2.02 ppm) and the two protons at C-2 position (3.08 ppm)] for the (*E*)-isomer. As such, the stereochemistry of the (*E*)-isomer was confirmed. The method could also be employed to the synthesis of γ-aryl-substituted β,γ-unsaturated acetamides with or without electron-donating substituents on the aryl groups (entries 4–11). Thus, the highly stereoselective (*E*)-alkenylborane generated from the hydroboration of terminal acetylenes with dicyclohexylborane gave stereoselective (*E*)-β,γ-unsaturated amides in moderate to good yields. The internal (*Z*)-styrylborane prepared from the hydroboration of 1,2-diphenylacetylene with dicyclohexylborane also underwent the Suzuki type cross-coupling reaction to give the desired product in about 54% yield (Eq. (1)). The plausible reaction mechanism could be similar to the one we have already described.[8] Thus, dibenzylideneacetone ligand was replaced initially by tricyclohexylphosphine to the palladium(0) catalyst, after oxidative addition with 2-bromo-*N*,*N*-dimethylacetamide to form bromopalladium enolate complex, the palladium complex was activated in the presence of a base. Another equivalent of base activated the alkenylborane to form a borate complex, which will undergo transmetallation with the activated palladium species to form alkenylpalladium enolate complex and a stablilized borate complex. Reductive elimination of the alkenylpalladium enolate complex afforded the cross-coupling product and regenerate Pd(0) catalyst.



(1)

Table 1. Synthesis of (*E*)-β,γ-unsaturated amides from terminal acetylenes



Entry	R =	Product yield (%)
1	$MeOCH_2$-	70
2	*n*-C_6H_{13}-	77
3	*n*-C_8H_{17}-	73
4	Ph-	65
5	*o*-Tolyl-	47
6	*m*-Tolyl-	51
7	*p*-Tolyl-	52
8		57
9		58
10		45
11		48

Since the highly stereoselective (*E*)-alkenylboranes are easily available, this method is useful for the synthesis of (*E*)-*N*,*N*-dimethyl-β,γ-unsaturatedacetamides.

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10. To a 100 mL round-bottomed flask with a rubber septum, from which was removed moisture and air under low pressure first and then flushed with dry nitrogen, was sequentially and slowly added 20 mL of dry THF, $Me_2S{\cdot}BH_3$ (10 mmol) and cyclohexene (20 mmol) at 0°C. The reaction mixture was stirred for another 3 h at 0°C. Terminal acetylene (10 mmol) was then slowly added to the above white reaction mixture at 0°C. The reaction mixture was stirred for another 3 h at rt until it became clear.
11. **NMR spectral data of selected products**:
(E)-N,N-Dimethyl-3-decenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 0.88 (t, $J=7.1$ Hz, 3H), 1.20–1.37 (m, 8H), 2.02 (m, 2H), 2.98 (s, 6H), 3.08 (d, $J=4.1$ Hz, 2H), 5.52–5.55 (m, 2H) ppm, ^{13}C NMR ($CDCl_3$, TMS) δ 14.07, 22.60, 28.84, 29.24, 31.70, 32.55, 35.45, 37.41, 37.91, 122.62, 134.04, 171.62 ppm.
(Z)-N,N-Dimethyl-3-decenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 0.88 (t, $J=7.1$ Hz, 3H), 1.20–1.37 (m, 8H), 2.02 (m, 2H), 2.98 (s, 6H), 3.10 (d, $J=4.1$ Hz, 2H), 5.52–5.55 (m, 2H) ppm.
(E)-N,N-Dimethyl-4-phenyl-3-butenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 2.98 (s, 3H), 3.07 (s, 3H), 3.31 (d, $J=6.5$ Hz, 2H), 6.36 (dt, $J=16.0$, 6.5 Hz, 1H), 6.47 (d, $J=16.0$ Hz, 1H), 7.20–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS) δ 35.50, 37.44, 38.06, 123.17, 126.19, 127.35, 128.46, 132.59, 136.98, 170.93 ppm.
(E)-N,N-Dimethyl-4-naphthalen-1-yl-3-butenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 3.00 (s, 3H), 3.12 (s, 3H), 3.42 (d, $J=6.8$ Hz, 2H), 6.38 (dt, $J=15.7$, 6.8 Hz, 1H), 7.21 (d, $J=15.7$ Hz, 1H), 7.41–8.11 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 35.57, 37.51, 38.44, 123.79, 123.99, 125.63, 125.67, 125.94, 126.41, 127.78, 128.49, 129.95, 131.07, 133.60, 134.79, 170.97 ppm.
(E)-N,N-Dimethyl-4-thiophen-2-yl-3-butenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 2.97 (s, 3H), 3.05 (s, 3H), 3.26 (d, $J=6.8$ Hz, 2H), 6.18 (dt, $J=15.8$, 6.8 Hz, 1H), 6.59 (d, $J=15.8$ Hz, 1H), 6.91–7.13 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 35.54, 37.48, 37.82, 122.79, 123.94, 125.10, 125.80, 127.19, 142.06, 170.68 ppm.
(E)-N,N-Dimethyl-5-methoxy-3-pentenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 2.95 (s, 3H), 3.02 (s, 3H), 3.15 (d, $J=6.6$ Hz, 2H), 3.33 (s, 3H), 3.91 (d, $J=6.0$ Hz, 2H), 5.65 (dt, $J=15.6$, 6.0 Hz, 2H), 5.88 (dt, $J=15.6$, 6.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 35.45, 37.31, 37.38, 72.77, 126.97, 129.50, 170.85 ppm.
(E)-N,N-Dimethyl-3-dodecenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 0.88 (t, $J=7.0$ Hz, 3H), 1.26–1.38 (m, 12H), 2.02 (m, 2H), 2.94 (s, 3H), 3.01 (s, 3H), 3.07 (d, $J=4.7$ Hz, 2H), 5.52–5.54 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 14.05, 22.64, 29.17, 29.25, 29.27, 29.43, 31.86, 32.53, 35.44, 37.39, 37.89, 122.60, 134.04, 171.63 ppm.
(E)-N,N-Dimethyl-4-(4-methoxyphenyl)-3-butenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 2.97 (s, 3H), 3.05 (s, 3H), 3.27 (d, $J=6.8$ Hz, 2H), 3.79 (s, 3H), 6.19 (dt, $J=15.9$, 6.8 Hz, 1H), 6.41 (d, $J=15.9$ Hz, 1H), 6.83 (d, $J=6.7$ Hz, 2H), 7.29 (d, $J=6.7$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 35.51, 37.45, 38.07, 55.26, 113.94, 120.92, 127.35, 129.92, 132.05, 159.09, 171.17 ppm.
(E)-N,N-Dimethyl-4-(4-methylsulfanylphenyl)-3-butenamide: ^{1}H NMR ($CDCl_3$, TMS) δ 2.47 (s, 3H), 2.97 (s, 3H), 3.05 (s, 3H), 3.28 (d, $J=6.4$ Hz, 2H), 6.30 (dt, $J=16.0$, 6.4 Hz, 1H), 6.41 (d, $J=16.0$ Hz, 1H), 7.18 (d, $J=8.4$ Hz, 2H), 7.28 (d, $J=8.4$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 15.86, 35.48, 37.41, 37.94, 122.66, 126.59, 126.68, 131.94, 134.06, 137.42, 170.90 ppm.