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Palladium-catalyzed Heck-type reaction of 2-chloro acetamides with olefins

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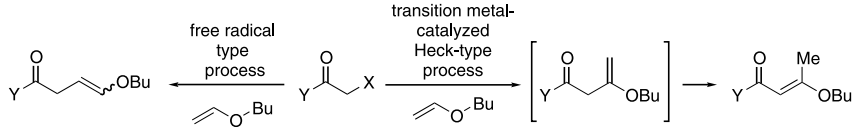
Abstract—Conditions have been developed for the palladium-catalyzed Heck-type reaction of 2-chloro acetamides with several olefins. The regiochemistry of the products obtained speaks in favor of an involvement of palladium enolates in this reaction.

The Heck reaction, the palladium-catalyzed arylation and vinylation of alkenes, has become a versatile tool in organic synthesis.[1] Considerable effort is directed towards expanding the scope of this important reaction. Even though the ability to make use of C_{sp3}–X compounds as substrates in the Heck reaction is highly desirable only a limited number of examples for this kind of process exists.[2] We figured that α-halocarbonyl compounds would represent a valuable enolate precursor for Heck-type reactions.[3] The related coupling of α-halocarboxylic acid derivatives with alkenes, through halogen atom transfer addition or cyclization reactions is a well known reaction.[4,5] However, this free radical based reactions have other characteristics and lead to other products than would be expected for a transition metal-catalyzed Heck-type reaction. For example, in the reaction of α-halocarboxylic acid derivatives with butyl vinyl ether a free radical type reaction gives rise to the linear product,[4e] while a transition metal-catalyzed Heck-type reaction should lead to the branched product (Scheme 1).

We started our investigation with the reaction of 2,3-dihydrofurane with 2-chloro *N*,*N*-diethyl acetamide (Table 1, entry 1). We were pleased to find that under optimized conditions,[6] using 5 mol% $Pd(PPh_3)_2Cl_2$ and iPr_2NEt as a base in CH_3CN at 110°C for 24 h, the desired Heck-type product is formed in 65% as a mixture of two easily separable double bond isomers. Interestingly, using 2-bromo *N*,*N*-diethyl acetamide led to the increased formation of side products and a reduced product yield of 30%.[6] For this reason we tested a number of other 2-*chloro* acetamides in the reaction with 2,3-dihydrofurane. Surprisingly, the unsubstituted chloro acetamide failed to react under our standard reaction conditions (entry 2). Gratifyingly, secondary 2-chloro amides gave yields of 67 and 75% (entries 3,4) and the reaction can conveniently be performed on a 5 mmol scale (entry 4). In all these cases, the α-position of the 2,3-dihydrofurane was attacked regioselectively, and the resulting product double bond isomers were easily separable by column chromatography. This regioselectivity renders a free radical mechanism unlikely and speaks in favor of an involvement of palladium-enolates in the catalytic cycle (Scheme 1).[4]

Opposite to the aforementioned cases bromo acetonitrile gave the *β-substituted* dihydrofurane **4** as the sole detectable isomer presumably formed by a free radical mechanism (Scheme 2). It is important to note that this



Scheme 1. Different reaction pathways for free radical type[4e] and transition metal-catalyzed Heck-type processes (X = halide).

Keywords: Heck reaction; 2-chloro acetamides; palladium.
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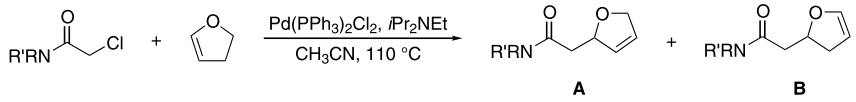
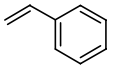
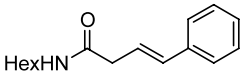
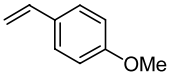
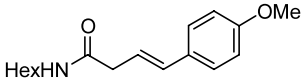
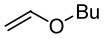
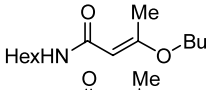
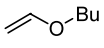
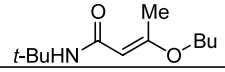
Table 1. Reaction of 2-chloro acetamides with 2,3-dihydrofurane[a]



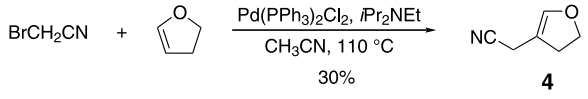
Entry	R	R′	Product	Yield (%)	Ratio **A**:**B**
1	Et	Et	**1**	65	65:35
2	H	H	–	–	–
3	*t*Bu	H	**2**	67	42:58
4	Hexyl	H	**3**	75[b]	51:49

[a] Reactions were run on a 0.44 mmol scale in sealed tubes under an argon atmosphere with 1 equiv. of 2-chloro *N*-hexyl acetamide, 5 equiv. of olefin, 0.05 equiv. of $PdCl_2(PPh_3)_2$, and 1.5 equiv. of *i*PrNEt in 1.5 mL of acetonitrile at 110°C for 24 h. The product isomers **A** and **B** were separated by column chromatography.[7]
[b] 71% yield were obtained on a 5 mmol scale.

Table 2. Reaction of mono-substituted olefins with 2-chloro *N*-hexyl acetamide[a]

Entry	Olefin	Isolated product		Yield (%)
1			(**5**)	39[b]
2			(**6**)	35[b]
3			(**7**)	53[c,d]
4[e]			(**8**)	63[c]

[a] Reactions were run on a 0.44 mmol scale in sealed tubes under an argon atmosphere with 1 equiv. of 2-chloro *N*-hexyl acetamide, 5 equiv. of olefin, 0.05 equiv. of $PdCl_2(PPh_3)_2$, and 1.5 equiv. of *i*PrNEt in 1.5 mL of acetonitrile at 110°C for 24 h.[7]
[b] Stereochemistry of the double bond of the styrene derivatives was assigned by comparison to literature data for related amides.[8]
[c] Stereochemistry of the double bond of the enol ethers was assigned based on a NOESY measurement.
[d] 50% yield were obtained on a 5 mmol scale.
[e] 2-Chloro *N*-*t*-butyl acetamide was used as substrate.

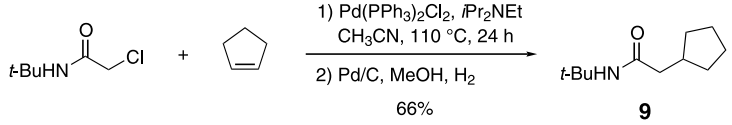


Scheme 2.

product was not detected in the crude reaction mixtures when 2-chloro acetamides were employed as starting materials (Table 1).

To demonstrate the scope of this new Heck-type reaction, we submitted a variety of mono-substituted olefins to the standard reaction conditions (Table 2). Styrene and an electron rich styrene derivative reacted with 2-chloro *N*-hexyl acetamide to give the linear products predominantly. Whereas in the case of styrene a significant amount of other isomers was formed (10%, entry 1), the *p*-methoxy styrene gave less than 3% of other isomeric products (entry 2). Similar to 2,3-dihydrofurane, butyl vinyl ether was attacked at the internal position giving rise to the branched regioisomer (entries 3, 4). This is in striking contrast to the regiochemistry observed in atom transfer radical additions of butyl vinyl ether in which the linear product is formed.[4e] The (*E*)-isomer was obtained in 53% yield as the major product along with a small amount (<5%) of the (*Z*)-isomer (entry 3). Performing the reaction on a 5 mmol scale gave a comparable result. In the same reaction 2-chloro *N*-*t*-butyl acetamide gave a remarkable 63% yield of the (*E*)-isomer (entry 4).

Finally, cyclopentene was found to be another useful substrate for this new Heck-type reaction with 2-chloro acetamides. Reaction with 2-chloro *N*-*t*-butyl acet-



Scheme 3.

amide afforded the Heck-product in 66% as an inseparable mixture of double bond isomers. Hydrogenation gave **9** in quantitative yield (Scheme 3).

In conclusion, we have found a new intermolecular palladium-catalyzed Heck-type process that allows the reaction of 2-chloro acetamides with several olefins. This transformation should increase the versatility of the Heck reaction even further.

Acknowledgements

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References

1. (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4; (b) Shibasaki, M.; Miyazaki, F. In *Handbook of Organo-Palladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1; (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (d) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
2. (a) Bräse, S.; Waeggell, B.; de Meijere, A. *Synthesis* **1998**, 148–152; (b) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253–259; (c) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725–727. For a cobalt-catalyzed Heck-type reaction of alkyl halides with styrenes, see: (d) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514–6515.
3. For the use of α-halo carbonyl derivatives in other palladium-catalyzed reactions, see: (a) Sato; M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405–1408; (b) Gooßen, L. J. *Chem. Commun.* **2001**, 669–670; (c) Lapidus, A. L.; Eliseev, O. L.; Bondarenko, T. N.; Sizan, O. E.; Ostapenko, A. G.; Beletskaya, I. P. *Synthesis* **2002**, 317–319; (d) Liu, X.-X.; Deng, M.-Z. *Chem. Commun.* **2002**, 622–623.
4. (a) Curran, D. P. *Synthesis* **1988**, 489; (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3157; (c) Giese, B.; Göbel, T.; Kopping, B.; Zipse, H. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme Verlag: Stuttgart, 1995; Vol. E 21c; (d) Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755–2757; (e) Curran, D. P.; Ko, S.-B. *Tetrahedron Lett.* **1998**, *39*, 6629–6632; (f) Wang, J.; Li, C. *J. Org. Chem.* **2002**, *67*, 1271–1276.
5. For a related palladium-catalyzed intramolecular cyclization of 2-bromo *N*-allylacetamides, see: Yang, S.-C.; Shea, F.-R. *J. Chin. Chem. Soc.* **1995**, *42*, 969–972.
6. Combined yields for both isomers: THF: <10%; toluene: <10%; *i*PrCN: 35%; DMF: 40%; $Pd(dppf)Cl_2$: <5%; $Pd(OAc)_2$: <5%; $Pd(OAc)_2$+PCy_3: <10%; $Pd_2(dba)_3$+P(*o*-furyl)$_3$: 48%; $Pd(PPh_3)_4$: 62%; no base: 0%; NEt_3: 36%; 2-bromo *N*,*N*-diethyl acetamide: 30%.
7. **Representative experiment**: A mixture of $Pd(PPh_3)_2Cl_2$ (15 mg, 0.022 mmol), CH_3CN (1.5 mL), butyl vinyl ether (284 μL, 2.19 mmol), *i*Pr_2NEt (114 μL, 0.656 mmol) and 2-chloro *N*-hexyl acetamide (77.6 mg, 0.437 mmol) was heated in a sealed tube to 110°C for 24 h. (**CAUTION**! The reactions were carried out under pressure. Take the necessary safety measures against explosion.) The reaction mixture was allowed to cool before the tube was carefully opened. MTBE (10 mL) was added and the solution was washed with sat. aq. $NaHCO_3$ (10 mL) solution. The aqueous layer was extracted with MTBE (2×10 mL), the combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 5:1) to afford **7** as a crystalline colorless solid (56 mg, 53%).

Spectroscopic data for representative compounds:

1A: yellowish oil; R_f=0.32 (EtOAc); IR (film) 3077, 2973, 2933, 2875, 1640, 1602, 1481, 1461, 1432, 1112, 1070, 949, 803, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97–5.94 (m, 1H, CH), 5.90–5.87 (m, 1H, CH), 5.27–5.21 (m, 1H, OCH), 4.67–4.56 (m, 2H, OCH_2), 3.45–3.28 (m, 4H, NCH_2), 2.68 (dd, J=6.3, 14.9 Hz, 1H, CH_2CO), 2.44 (dd, J=6.7, 14.9 Hz, 1H, CH_2CO), 1.15 (t, J=7.1 Hz, 3H, CH_3), 1.10 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (CO), 130.1 (CH), 126.5 (CH), 83.3 (OCH), 74.9 (OCH_2), 42.0 (CH_2), 40.0 (CH_2), 39.8 (CH_2), 14.2 (CH_3), 13.1 (CH_3); MS (EI), m/z (%) 183 (M^+, 100), 115 (51), 111 (45), 100 (96), 86 (20), 72 (45), 69 (38), 58 (33); HRMS (EI) calcd for $C_{10}H_{17}NO_2$: 183.1259, found 183.1260.

1B: yellowish oil; R_f=0.51 (EtOAc); IR (film) 3095, 2973, 2933, 2874, 1641, 1461, 1140, 1053, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (q, J=2.5 Hz, 1H, OC*H*CH), 5.02 (dq, J=6.8, 10.1 Hz, 1H, OC*H*CH_2), 4.88 (q, J=2.5 Hz, 1H, OCHC*H*), 3.43–3.28 (m, 4H, NCH_2), 2.88 (ddt, J=2.4, 10.1, 13.1 Hz, 1H, CH_2CHCH), 2.81 (dd, J=6.4, 15.3 Hz, 1H, CH_2CO), 2.49 (dd, J=6.8, 15.3 Hz, 1H, CH_2CO), 2.31 (ddt, J=2.4, 7.1, 15.4 Hz, 1H, CH_2CHCH), 1.17 (t, J=7.1 Hz, CH_3), 1.11 (t, J=7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (CO), 144.6 (O*C*HCH), 99.2 (OCH*C*H), 78.3 (O*C*HCH_2), 42.0 (CH_2), 40.0 (CH_2), 39.3 (*C*H_2CO), 35.1 (*C*H_2CHCH), 14.3 (CH_3), 13.1 (CH_3); MS (EI), m/z (%) 183 (M^+, 1), 115 (100), 100 (52), 86 (23), 72 (72), 69 (12), 58 (40); HRMS (EI) calcd for $C_{10}H_{17}NO_2$+H: 184.1338, found 184.1337.

4: colorless oil; R_f=0.40 (hexane/EtOAc 2:1); IR (film) 3096, 2966, 2899, 2860, 2249, 1668, 1414, 1272, 1103, 981, 865, 736; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.32 (quint, J=1.7 Hz, 1H, OCH), 4.40 (t, J=9.6 Hz, 2H, OCH_2), 3.14 (q, J=1.2 Hz, 2H, CH_2CN), 2.65 (m, 2H, CH_2CH_2O); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 144.0 (OCH), 117.3 (CN), 103.9 (C), 70.7 (OCH_2), 31.7 (*C*H_2CH_2O), 15.4 (*C*H_2CN); MS (EI), m/z (%) 109 (M^+, 63), 80 (38), 69 (27), 54 (100); HRMS (EI) calcd for C_6H_7NO: 109.0528, found 109.0529.

5: white, crystalline solid; R_f=0.35 (hexane/EtOAc 1:1); IR (KBr) 3248, 3081, 2954, 2926, 2857, 1631, 1561, 1495, 1450, 1251, 965, 756, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 5H, CH_{Ar}), 6.53 (d, J=15.8 Hz, 1H, C*H*CHCH_2), 6.29 (dt, J=7.3, 15.8 Hz, 1H, CHC*H*CH_2), 5.63 (s, 1H, NH), 3.25 (m, 2H, CH_2N), 3.15 (dd, J=1.3, 7.3 Hz, 2H, CH_2CH), 1.53–1.46 (m, 2H, NCH_2CH_2), 1.32–1.27 (m, 6H, $CH_3CH_2CH_2CH_2$), 0.89–0.86 (m, 3H,

CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (CO), 136.6 (C_{ipso}), 134.5 ($CHCHCH_2$), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 126.2 (CH_{Ar}), 122.6 ($CHCHCH_2$), 40.9 (CH_2CH), 39.7 (CH_2N), 31.4 (CH_2), 29.5 (NCH_2CH_2), 26.5 (CH_2), 22.5 (CH_2), 13.9 (CH_3); MS (EI), m/z (%) 245 (M^+, 10), 118 (100), 115 (14), 91 (7), 85 (17), 57 (5); HRMS (EI) calcd for $C_{16}H_{23}NO$: 245.1780, found 245.1780.

7: white, crystalline solid; $R_f = 0.74$ (EtOAc); IR (KBr) 3282, 3075, 2956, 2931, 2870, 1657, 1610, 1551, 1471, 1281, 1203, 1070, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H, NH), 4.87 (s, 1H, CHCO), 3.69 (t, $J = 6.6$ Hz, 2H, OCH_2), 3.20 (dt, $J = 6.0$, 7.2 Hz, 2H, NCH_2), 2.25 (d, $J < 0.5$ Hz, 3H, CCH_3), 1.70–1.63 (m, 2H, OCH_2CH_2), 1.51–1.37 (m, 4H, NCH_2CH_2, $OCH_2CH_2CH_2$), 1.34–1.29 (m, 6H, $NCH_2CH_2CH_2CH_2CH_2$), 0.94 (t, $J = 7.4$ Hz, 3H, $OCH_2CH_2CH_2CH_3$), 0.91–0.87 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 ($COBu$), 167.4 (CO), 93.8 ($CHCO$), 67.7 (OCH_2), 39.6 (NCH_2), 32.0 ($CH_2CH_2CH_3$), 31.2 (OCH_2CH_2), 30.3 (NCH_2CH_2), 27.1 ($NCH_2CH_2CH_2$), 23.0 (CH_2CH_3), 19.6 ($OCH_2CH_2CH_2$), 18.5 (CCH_3), 14.2 (CH_2CH_3), 13.9 ($OCH_2CH_2CH_2CH_3$); MS (EI), m/z (%) 241 (M^+, 12), 226 (10), 198 (40), 184 (13), 171 (6), 156 (6), 141 (37), 128 (7), 115 (11), 100 (11), 85 (100), 69 (6), 57 (11); HRMS (EI) calcd for $C_{14}H_{27}NO_2$: 241.2042, found 241.2044.

9: white, crystalline solid; $R_f = 0.65$ (hexane/EtOAc 1:1); IR (film) 3278, 3200, 3079, 2955, 2867, 1641, 1556, 1452, 1362, 1227, 1134, 704; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H, NH), 2.25–2.14 (m, 1H, CH), 2.08–2.05 (m, 2H, $COCH_2$), 1.84–1.77 (m, 2H, $CHCH_2CH_2$), 1.65–1.50 (m, 4H, $CHCH_2CH_2$), 1.33 (s, 9H, CH_3), 1.17–1.08 (m, 2H, $CHCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (CO), 51.0 (C), 44.0 ($COCH_2$), 37.3 (CH), 32.4 ($CHCH_2CH_2$), 28.8 (CH_3), 24.9 ($CHCH_2CH_2$); MS (EI), m/z (%) 183 (M^+, 0.3), 128 (15), 115 (29), 83 (5), 69 (5), 58 (100); HRMS (EI) calcd for $C_{11}H_{22}NO$: 184.1701, found 184.1701.

8. (a) Imada, Y.; Shibata, O.; Murahashi, S.-I. *J. Organomet. Chem.* **1993**, *451*, 183–194; (b) Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721–1740.