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Microwave-Promoted and Chelation-Controlled Double Arylations of Terminal Olefinic Carbon of Vinyl Ethers

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Herein we report a rapid, palladium-catalyzed terminal diarylation of the chelating olefin *N*,*N*-dimethyl(2-ethenyloxy)ethanamine under noninert conditions utilizing controlled microwave heating as a convenient energy source. Among the aryl bromides examined, both electron-rich and electron-poor substrates were demonstrated to furnish useful yields after only 10−120 min of directed microwave heating at 160−200 °C. The good terminal regioselectivity suggests that the precatalyst (Herrmann's palladacycle) serves as a source of weakly coordinated palladium(0) in the investigated high-temperature Heck process.

The Heck arylation of carbon−carbon double bonds is mediated by a variety of Pd(0) and Pd(II) catalyst precursors, although the nature of the "true" catalyst is still under debate.[1,2] In general, the Heck coupling of aryl halides with both electron-rich and electron-poor terminal alkenes affords monoarylated products.[3−6] With electron-deficient olefins under harsh reaction conditions, such as with excess of the aryl halide[7] or under high pressure,[8] a 2-fold terminal arylation to give 1,1-diarylalkene derivatives may occur.[5] Alternatively, the olefin may be equipped with a catalyst-directing functionality that increases the reactivity of the double bond.[9−12] In a recent article from our laboratory, the introduction of a specific, palladium-coordinating dimethylamino group allowed for regioselective, terminal β,β-diarylation of the acyclic vinyl ether **1** with aryl iodides.[13]

We were interested in further studies of regioselective double terminal arylations of vinyl ethers for two reasons. First, these are precursors to synthetically valuable diaryl substituted acetaldehydes, and second, pharmacophores consisting of a diarylmethine group linked to a dimethylamine moiety through a spacer are very abundant in the present flora of therapeutic agents. Thus, this new class of compounds has potential for medicinal applications.[14] A series of GABA uptake inhibitors have also been reported with similar structures.[15]

The combination of transition-metal catalysts and microwave heating is not only a hot topic but also an area that is likely to have an impact on several fields of modern chemistry.[16,17] The palladium-catalyzed coupling reaction that with classical heating typically needs days to reach completion can now with high reproducibility be brought to full conversion in only minutes, consuming only a fraction of the energy that normally is needed for a standard, oil bath-heated reaction.[18] To reach maximum catalyst activity, it is desirable to go beyond the boiling point of the employed solvent. These superheating conditions can be easily obtained with modern single-mode microwave equipment supplied with temperature and pressure controlling devices. In addition, the preparative potential of this methodology has increased with the rapid development of catalytic systems that can withstand the sometimes extreme temperatures that are induced under irradiation.[19] Herrmann's Pd(II)-phosphapalladacycle **3**[20] is an excellent thermostable precata-

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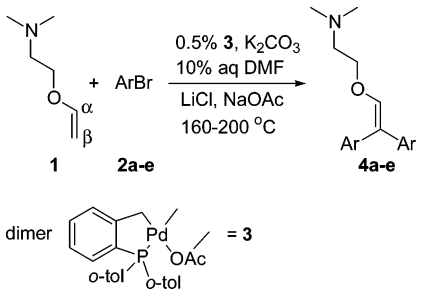
SCHEME 1



lyst in Heck chemistry for both aryl triflates and aryl bromides **2**, although nonactivated aryl chlorides react only reluctantly.[1] Furthermore, no aryl migration or ligand decomposition occurs at 150 °C, allowing for recovery of unchanged dimeric palladacycles in yields up to 70%.[1] The catalyst can, as a consequence, be recycled with little loss of activity.[1] Despite these outstanding characteristics, mechanistic details about this class of catalysts still remain partly obscure. The fact that aryl palladium(IV) complexes do exist stimulated the suggestion that an alternative redox cycle involving Pd(II)/Pd(IV) had to be taken into account.[21−23] Recent investigations by Herrmann and Beller, however, also support the classic Pd(0)/Pd(II) interconversion with phosphapalladacycles as precatalysts.[1,22]

We have now developed a rapid protocol for microwave-assisted regioselective double β-arylations of the chelating vinyl ether *N*,*N*-dimethyl(2-ethenyloxy)ethanamine (**1**) using palladacycle **3** as the palladium source. We demonstrate that by proper selection of experimental parameters, it is possible to achieve symmetrical and nonsymmetrical terminal β,β-diarylations with both electron-rich and electron-poor aryl bromides.

To achieve diarylation, we planned to take advantage of the fact that intramolecular reactions, in general, proceed faster than their intermolecular counterparts. In a previous paper,[13] we disclosed that the dimethylaminoethyl group in **1** not only promoted high regioselectivity in the Heck synthesis of the β,β-diarylation products from aryl iodides, but also that chelating olefins reacted faster than a nonchelating alkyl vinyl ether derivative. We suggested that the improved reactivity was due to an initial nitrogen coordination to the aryl palladium species prior to π-intermediate formation.[13] The oxidative addition complex is thus presented for the double bond in a "pseudo-intramolecular" process, accelerating the π-complex formation and the subsequent migratory insertion.

Symmetric Products. One-pot microwave-heated bisarylations of unsubstituted **1** were carried out in sealed vessels under air employing an excess of the aryl bromide (3.0−5.0 equiv) with a low amount of palladacycle **3** (0.5 mol %) in 10% aqueous DMF (Scheme 1). To increase the stability of the underligated catalytic Pd(0) system, a highly ionic reaction cocktail was preferred using lithium chloride (2.0 equiv) and sodium acetate (1.35 equiv) as additive and potassium carbonate as base (2.2 equiv). For each individual bisarylation, several reaction temperatures were explored. Irradiation times from 5 min to 6 h were evaluated. Five different aryl bromides (**2a**−**e**) were selected since earlier studies had established that the electron density and the substitution pattern of the aryl moiety had a critical effect on the regioselectivity in monoarylations of vinyl ethers.[9] Selected preparative results obtained during these studies are summarized in Table 1. The final diarylated products **4** were fully purified from the α,β-isomers in all reactions, while the intermediate monoarylated **5** products were never isolated.

TABLE 1. Symmetric One-Pot Chelation-Controlled Microwave-Promoted β,β-Diarylation of 1

entry	Ar[a]	temp (°C)	time[b] (min)	product	α,β/**4**[c]	isolated yield (%)[d]
1	*p*-MeO−Ph−	160	10	**4a**	8/92	38
	2a	180	10		6/94	52
		200	10		7/93	45
2	*o*-Me−Ph−	160	55	**4b**	5/95	80
	2b	180	55		5/95	69
3	Ph−[e]	160	20	**4c**	10/90	65
	2c	180	10		10/90	67
		180[f]	10		10/90	63
4	*p*-Cl−Ph−	160	55	**4d**	12/88	59[g]
	2d	180	30		12/88	55[g]
		200	10		14/86	46[g]
5	*p*-OCH−Ph−	160[h]	360	**4e**	23/77	9
	2e	180[h]	55		29/71	36

[a] 5 equiv of **2**. [b] >95% conversion of **1** and **5** by GC−MS. [c] Determined by GC−MS and ^{1}H NMR. [d] Yield of the β,β-product **4** (no α,β-isomer), >95% purity by GC−MS. [e] Only 3 equiv of **2c**. [f] Conventional heating with an oil bath. [g] 10−15% 4,4′-dichlorostilbene detected by GC−MS. [h] Remaining **5e**.

In contrast to most Heck arylations with electron-poor olefins, but in accordance with previous results with vinyl ethers, the electron-rich and neutral **2a**−**c** afforded good two-step yields of terminally diarylated product **4a**−**c** (entries 1−3, Table 1). Even the orthosubstituted **2b**, whose vinylation might be sterically problematic, was efficiently converted into the desired β,β-bisarylated product **4b** with high yield and regioselectivity. Classic heating at 180 °C furnished almost identical reaction results as microwave heating (entry 3). Successful chemoselective activation of the bromosubstituent on **2d** produced good yields at all investigated temperatures. Full conversion of the monoarylated intermediate **5** was obtained in all cases except for *p*-bromobenzaldehyde **2e**. In fact, all formyl-functionalized compounds (**2e**, **5e**, and **4e**) underwent a competing reductive amination process under the employed high-temperature conditions, forming the corresponding *N*,*N*-dimethylbenzylamine byproducts. Since it is known that DMF may act as a combined dimethylamine and carbon monoxide source, vinylation of **2e** was also investigated using DMAc as a more thermostable alternative to DMF.[24] Unfortunately, this change of solvent consistently afforded lower isolated yields. It is notable that in all entries the bisarylation occurred with high regioselectivity at the terminal β-carbon (α,β/**4** < 14:86) and that only minor amounts of biaryl and stilbene derivatives were formed. The regioselectivity was also found to be largely independent of the reaction temperature permitting fast reactions (down to 10 min)

(20) *trans*-Di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (II). Registry number provided by the author: 172418-32-5.
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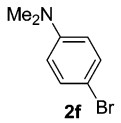
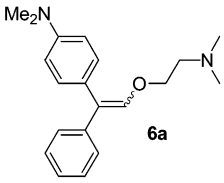
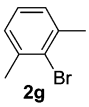
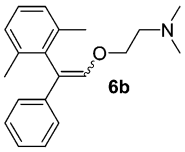
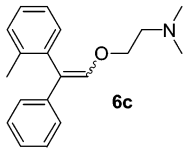
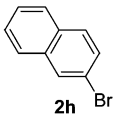
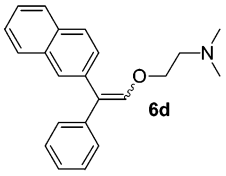
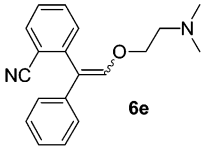
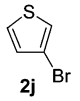
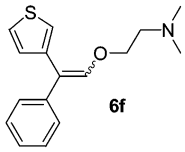
TABLE 2. Chelation-Controlled Microwave-Promoted *β*-Arylation of Monoarylated Vinyl Ether 5

Entry	ArBr	Olefin 5	Equiv ArBr	Temp (°C)	Time (min)	β,β-Diarylated Vinyl Ether 6	α,β/β,β[a]	*E*/*Z*[b]	Isolated Yield of 6 (%)[c]
1	 **2f**	**5a**	2	160	120	 **6a**	5/95	44/56	32
			2	180	55		5/95	29/71	41
			2	200	30		7/93	29/71	39
2	 **2g**	**5a**	5	200	120	 **6b**	14/86	73/27	25[d]
3	**2b**	**5a**	5	160	20	 **6c**	4/96	29/71	75
			5	180	10		6/94	30/70	65
			5	200	10		6/94	30/70	64
4	 **2h**	**5a**	2	180	20	 **6d**	3/97	31/69	62
			2	200	10		3/97	29/71	62
5	**2c**	**5b**	2	160	55	**6d**	3/97	65/35	60
			2	180	15		6/94	65/35	73
6	 **2i**	**5a**	5	160	360	 **6e**	2/98	23/77	41
			5	180	120		3/97	22/78	47
			5	200	55		2/98	22/78	42
7	 **2j**	**5a**	5	180	120	 **6f**	7/93	26/74	49
			5	200	55		9/91	28/72	43
8	**2c**	**5a**	2	160	20	**4c**	6/94		64
			2	180	10		6/94		68

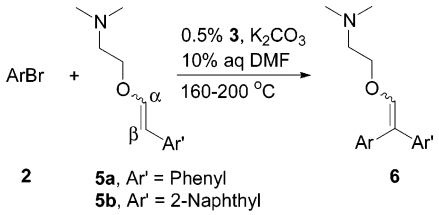
[a] Determined by GC−MS and ^{1}H NMR. [b] Determined for the *β*,*β*-product **6** by GC−MS and NOE experiments. [c] Combined yield of the *E*- and *Z*-isomers (no α,*β*-product), >95% purity by GC−MS. [d] Performed in DMAc.

at very high temperatures (160−200 °C) without reduced regioselectivity. The exception concerns the very sluggish and less selective vinylation of the electron-deficient **2e** (entry 5).

Unsymmetrical Products. A series of aryl bromides (**2**) was reacted with *β*-arylated olefins **5a,b** under air using almost identical reaction conditions as those employed in the symmetrical examples (Scheme 2). The mono *β*-phenylated, pure **5a** was selected as the standard olefin for the sequential, unsymmetrical protocol to assess the productivity and selectivity of the second arylation. The preparative results are presented in Table 2.

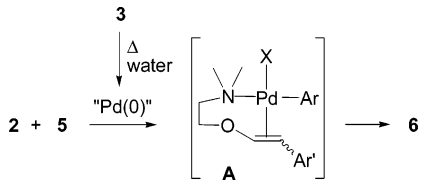
The geometrical isomers of unsymmetric *β*,*β*-products **6**, except **6a**, were all readily separable on silica column and characterized as the individual compounds. However, the isolated yields are in all cases reported for the diastereomeric *E*/*Z*-mixtures. Slightly electron-rich (**2b**) or neutral (**2h** and **2c**) delivered the best yields in the study accompanied with good *β*,*β*-selectivity (entries 3−5, Table 2). The electron-poor substrate **2i** furnished the best terminal selectivity, which is in accordance with the preference for electron-deficient aryl groups to migrate to the most electron-rich (*β*) vinyl carbon in the insertion step.[25] The selectivities were in all cases high (α,*β*/*β*,*β* < 9:91), except for the sterically very hindered 2,6-dimethyl-

SCHEME 2



2 **5a**, Ar' = Phenyl; **5b**, Ar' = 2-Naphthyl **6**

SCHEME 3



substituted **2g** (entry 2). The somewhat lowered β-selectivity and the poor yield encountered with **2g** is probably a consequence of steric congestions in the insertion step, requiring high temperature and long reaction time. The broad scope of aryl substrates usable in the Heck reaction manifests itself in the reactions with electron-rich *N*,*N*-dimethylamino-substituted **2f** and heteroaromatic **2j**, both delivering usable yields (entries 1 and 7). As experienced in the one-pot arylations (Table 1), the selectivities and yields in Table 2 were rather insensitive to the employed reaction temperatures allowing for high-temperature reactions with reaction times down to only 10 min (entries 3, 4, and 8, Table 2). The last introduced aryl substituent preferred the *Z*-position in all cases. Thus, by switching the order of arylation, the opposite geometrical isomer of **6d** could be preferentially synthesized (entries 4 and 5, Table 2). The introduction of a second phenyl group to monophenylated **5a** (entry 8, Table 2) proceeded with a higher β,β-selectivity than the one-pot double phenylation procedure starting directly from **1** (entry 3, Table 1). The reduced performance of the tandem arylation is possibly explained by a catalytic aging process (e.g., Pd-black formation), rendering the second phenylation in the one-pot protocol less regioselective.

The potential for **3** to catalyze chelation-controlled regioselective β,β-arylations of vinyl ethers was illustrated in the previous section. Whereas the preparative advantages are clear, the oxidation state of the active metal is not obvious. The square planar 16e$^-$ π-species **A** is commonly accepted as key intermediate with the Pd(0)/Pd(II) redox mechanism, directing the insertion via chelation to afford terminal arylation (Scheme 3).[6,13] With a Pd(II)/Pd(IV)-based catalytic cycle, a possible nitrogen-coordinated octahedral alkeneic Pd(IV) π-intermediate must be postulated before the regiocontrolling migratory insertion step. If the Pd(II)/Pd(IV) pathway was active, and not the more widely recognized Pd(0)/Pd(II) route, some difference in regioselectivity should be expected. Performing the reactions with classic Pd(0)-generating standard precatalysts such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/P(o\text{-tol})_3$, or $Pd(PPh_3)_2Cl_2$ does not give any substantial difference in stereo- or regioselectivity,[26] but only in conversion and yield. Furthermore, Herrmann has reported a similar distribution of isomers in the Heck arylation of nonchelating butyl vinyl ether with both palladacycle **3** and with classic $Pd(OAc)_2$.[27]

Early attempts to develop a high-speed microwave protocol for β,β-diarylation of **1** revealed that water addition was crucial for catalyst activity.[28] It was further found that decreased catalyst loading afforded better results.[29] We believe that the high regiocontrol indicates that **3** acts as a catalyst reservoir[30] for Pd(0) and that the release of the underligated metal(0) is accelerated by water under our high-temperature conditions (Scheme 3). In addition, the aggregation rate of Pd(0) is probably of higher order than the reaction rate, since lowering the catalytic load prolongs the active catalyst lifetime.

We have shown that diverse aryl bromides can be used in microwave-heated, chelation-controlled diarylations of vinyl ethers. Thus, the metal presenting dimethylaminoethyl group does not only provide high β,β-selectivity at high reaction temperatures, but also enhances the reactivity of the double bond. We strongly believe that the concept of chelation-promoted multiarylations can be successfully applied also to cyclic Heck substrates. Finally, with support from the obtained high regioselectivity we postulate a traditional Pd(0)/Pd(II) catalytic cycle with Herrmann's palladacycle serving as an efficient palladium(0) source.

Experimental Section

General Procedure for Symmetric Diarylations (Table 1). The following chemicals were added to a thick-walled tube: **3** (3.2 μmol, 3.0 mg), LiCl (1.32 mmol, 56.0 mg), NaOAc (0.880 mmol, 72.2 mg), K_2CO_3 (1.43 mmol, 198 mg), aryl bromide **2** (quantity according to entry), olefin **1** (0.651 mmol, 75.0 mg), DMF (2 mL), and water (0.20 mL). The tube was then sealed under air, and the contents were magnetically stirred and microwave-heated at a specified temperature for an appropriate time (see Table 1 for details). After cooling, the reaction mixture was diluted with dietyl ether and washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted three times with diethyl ether. The etheral phases were combined and dried with K_2CO_3 (s). After evaporation of the solvent, silica column chromatography was performed using gradient elution (Et_2O/isohexane) containing triethylamine (1%).

***N*,*N*-Dimethyl-2-[(2,2-di-*p*-anisyl)ethenyloxy]ethanamine (4a).** Yellowish oil, 52% yield (0.111 g, reaction performed at 180 °C, 10 min, >95% by GC−MS). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.9 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.40 (s, 1H), 4.01 (t, J = 6.1 Hz, 2H), 3.81 (s, 6H), 2.65 (t, J = 6.1 Hz, 2H), 2.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 158.2, 143.8, 133.4, 131.1, 130.7, 129.7, 119.9, 113.9, 113.4, 71.8, 58.9, 55.44, 55.35, 46.3. MS *m*/*z* (relative intensity 70 eV): 327 (M^+, 18), 72 (100), 58 (25). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70. Found: C, 73.3; H, 7.8.

General Procedure for Nonsymmetric Diarylations (Table 2). The following chemicals were added to a thick-walled tube: **3** (3.2 μmol, 3.0 mg), LiCl (1.32 mmol, 56.0 mg), NaOAc (0.880 mmol, 72.2 mg), K_2CO_3 (0.782 mmol, 108 mg), aryl bromide (quantity according to entry), olefin **5** (0.65 mmol), DMF (2.0 mL), and water (0.2 mL). The tube was then closed under air, and the contents were magnetically stirred and microwave-heated at the temperature and time specified in Table 2. After cooling, the reaction mixture was diluted with dietyl ether, and washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted three times with diethyl ether. The etheral phases were combined and dried with K_2CO_3 (s). After evaporation of the solvent,

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(26) For selectivity values with the different catalytic systems, see the Supporting Information.
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silica column chromatography was performed using gradient elution (Et_2O/isohexane) containing triethylamine (1%).

***N,N*-Dimethyl-2-[(2-phenyl-2-(2-naphthyl))ethenyloxy]-ethanamine (6d).** Colorless oil, 62% yield (0.128 g, reaction performed at 180 °C, 20 min, >95% by GC−MS). Major isomer: (*Z*)- first GC−MS peak, first eluted on column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.72−7.62 (m, 3H), 7.50−7.45 (m, 1H), 7.36−7.30 (m, 2H), 7.25−7.13 (m, 5H), 6.51 (s, 1H), 3.96 (t, J = 5.9 Hz, 2H), 2.56 (t, J = 5.9 Hz, 2H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 140.9, 135.6, 133.7, 132.6, 130.3, 129.1, 128.7, 128.6, 128.3, 127.8, 127.5, 126.8, 126.0, 125.8, 120.9, 72.2, 59.0, 46.4. MS *m*/*z* (relative intensity 70 eV): 317 (M^+, 11), 215 (10), 72 (100), 58 (55). Minor isomer: (*E*)- second GC−MS peak, second eluted on chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75−7.64 (m, 3H), 7.59 (s, 1H), 7.40−7.32 (m, 4H), 7.29−7.13 (m, 4H), 6.57 (s, 1H), 3.99 (t, J = 6.1 Hz, 2H), 2.59 (t, J = 6.1 Hz, 2H), 2.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 138.4, 137.9, 133.9, 132.6, 130.3, 128.3, 128.1, 128.0, 127.9, 127.4, 126.9, 126.8, 126.4, 125.8, 121.0, 72.2, 59.0, 46.4. MS *m*/*z* (relative intensity 70 eV): 317 (M^+, 12), 215 (8), 72 (100), 58 (54). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30. Found: C, 82.9; H, 7.1.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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