DOI: 10.1002/adsc.201000493

Mizoroki–Heck Reactions with 4-Phenoldiazonium Salts

Bernd Schmidt,[a,*] Frank Hölter,[a] René Berger,[a] and Sönke Jessel[b]

[a] Institut für Chemie, Universität Potsdam, Karl-Liebknecht-Straße 24–25, Haus 25, 14476 Golm, Germany
Fax: (+49)-331-977-5059; e-mail: bernd.schmidt@uni-potsdam.de
[b] IP Bewertungs AG (IPB), Stephansplatz 10, 20354 Hamburg, Germany

Received: June 25, 2010; Published online: September 23, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000493.

Abstract: Significantly better yields were achieved in Mizoroki–Heck reactions using 4-phenoldiazonium salts instead of their *O*-alkylated analogues under otherwise identical conditions. We found that a one-flask deacetylation–diazotation–precipitation sequence starting from paracetamol or acetanilides derived thereof provides a convenient access to the required diazonium tetrafluoroborates. The utility of these arylating agents in palladium-catalyzed C–C bond forming reactions was demonstrated for a one-flask-synthesis of the heterocyclic core of the drug aripiprazole. Notably, the diazonium salt formation from an acetanilide could be combined with two Pd-catalyzed steps in a one-flask sequence, without any exchange of solvents or isolation of intermediates.

Keywords: diazo compounds; Heck reaction; homogeneous catalysis; palladium; phenols

Introduction

Functionalized aromatic systems, in particular phenols, are structural elements of outstanding importance in natural products,[1–3] drugs,[4] and drug candidates.[5] Apart from photochemical and radical reactions, additions of polar organometallics to carbonyl compounds and transition metal-catalyzed coupling and cross-coupling reactions[6] are commonly used synthetic methods in this field.[7] In this context, the Mizoroki–Heck reaction[8] is one of the most important transformations. Normally, aryl halides, triflates, or nonaflates[9] are coupled with an alkene in the presence of a Pd(0) catalyst (or an appropriate precursor), a ligand and a base. Although it had been discovered several decades ago by Matsuda et al. that arenediazonium salts[10] may also serve as arylating agents,[11] the number of examples has remained rather limited, compared to the literature published on Pd-catalyzed coupling reactions in general.[12–24] Among the most remarkable features of Mizoroki–Heck reactions with arenediazonium salts, sometimes referred to as Matsuda–Heck reactions, is the high reactivity at ambient temperatures and the opportunity to use simple recoverable catalysts such as palladium on charcoal in many cases.[22] Quite intriguing is the observation that many Pd-catalyzed reactions with arenediazonium salts do not only tolerate base-free conditions,[25] but sometimes give significantly better results in the absence of a base and a ligand, as demonstrated by Felpin et al.[26]

We have recently investigated the intermolecular Mizoroki–Heck reaction of cyclic enol ethers with the electron-rich alkoxyarenediazonium tetrafluoroborate **1a**.[27,28] The reaction is highly *trans*-diastereoselective and occurs without undesired double bond migration reactions, enabling a stereodivergent synthesis of all stereoisomers of the natural product centrolobine.[29] With a view towards the synthesis of the closely related bisphenol natural product de-*O*-methylcentrolobine, we synthesized the benzyl-protected diazonium salt **1b** with the intention to remove the benzyl protecting group after the Pd-catalyzed transformation by hydrogenation. **1b** and a number of other *O*-alkylated derivatives were obtained *via* a one-flask deacetylation–diazotation sequence from paracetamol and other substituted acetanilides.[30] While this approach was eventually successful,[31] considerable experimentation was required to find suitable conditions for the debenzylation step. These problems provoked the interesting question if a phenol protecting group is actually necessary for Pd-catalyzed transformations with arenediazonium salts. A literature search revealed that examples for Mizoroki–Heck reactions or related transformations are known for iodophenols,[32–34] but that in most cases *O*-alkylated derivatives were used, which were dealkylated after the Pd-catalyzed step.[35] Mizoroki–Heck reactions or related transformations

with phenoldiazonium salts are even less common,[36,37] and have, to the best of our knowledge, never been systematically investigated. In this contribution we present our efforts directed at the use of various phenoldiazonium salts as arylating agents in Mizoroki–Heck reactions. The performance of these reagents and their *O*-alkylated analogues is compared.[38]

Results and Discussion

Synthesis of Phenoldiazonium Salts

4-Phenoldiazonium chloride (**1c-Cl**) was first synthesized in 1896 by diazotation of 4-aminophenol.[39] Several decades later, it was reported that the tetrafluoroborate **1c** is not isolable.[40] This, however, turned out to be incorrect, since **1c** was later successfully obtained by diazotation of 4-aminophenol in concentrated HBF_4.[41] Recently, an interesting alternative approach to phenoldiazonium salts based on the dealkylation of alkoxyarenediazonium salts was published.[42] The 4-phenoldiazonium cation is easily deprotonated[43] to a phenolate **1c′**, which is more accurately described as a quinone diazide **1c″**, based on spectroscopic and theoretical investigations (Figure 1).[43–48] Quinone diazides such as **1c″** were found to undergo dediazonation to carbenes,[49] which has been exploited for photochemical C–C bond-forming reactions.[50]

We found that several 4-phenoldiazonium salts, including the simple derivative **1c**, are advantageously prepared from acetanilides rather than anilines, because many anilines are sensitive to oxidation. Contamination of the starting aniline with impurities resulting from oxidation leads to significantly lower yields and purities of the diazonium salts. Therefore, the phenolacetanilides **2c**, **e**, **g**, **i** were subjected to the conditions of the aforementioned one-flask deacetylation–diazotation–precipitation sequence.[30,31] The same method has previously been used by us for the synthesis of *O*-alkylated arenediazonium salts **1a**, **b**, **d**, **f**, **h**.[31] The carboxylic acid and ester-substituted derivatives **1j–l** were more conveniently obtained from the corresponding anilines by diazotation with $NaNO_2$ in HBF_4 (Table 1).

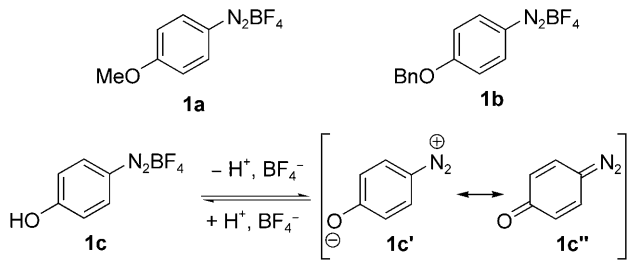
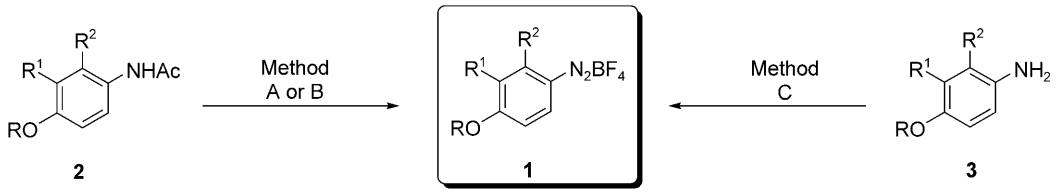


Figure 1. Alkoxyarene diazonium salts **1a**, **b** and 4-phenoldiazonium salt **1c**.

Mizoroki–Heck Reactions with Methyl Acrylate

First, we investigated Mizoroki–Heck reactions of diazonium tetrafluoroborates **1a–c** with methyl acrylate.

Table 1. Synthesis of phenoldiazonium salts **1**.



Entry	Starting material	R	R^1	R^2	Method[a]	Diazonium salt	Yield	Reference
1	**2a**	Me	H	H	A	**1a**	83%	[31]
2	**2b**	Bn	H	H	B	**1b**	71%	[31]
3	**2c**	H	H	H	A	**1c**	72%	this work
4	**2d**	Me	NO_2	H	B	**1d**	72%	[31]
5	**2e**	H	NO_2	H	B	**1e**	78%	this work
6	**2f**	Me	H	NO_2	B	**1f**	92%	[31]
7	**2g**	H	H	NO_2	B	**1g**	–[b]	this work
8	**2h**	Me	Br	H	B	**1h**	39%	[31]
9	**2i**	H	Br	H	B	**1i**	80%	this work
11	**3k**	H	CO_2H	H	C	**1k**	70%	this work
12	**3l**	Me	CO_2Me	H	C	**1l**	71%	this work
13	**3m**	H	CO_2Me	H	C	**1m**	94%	this work

[a] *Reagents and conditions:* Method A: HBF_4 (aqueous), 2-propanol, 90 °C; $NaNO_2$, 0 °C. Method B: BF_3·MeOH, MeOH, 60 °C; *tert*-BuONO, –15 °C. Method C: HBF_4 (aqueous), $NaNO_2$, 0 °C.

[b] **1g** is soluble in methanol and was used in solution for further transformations.

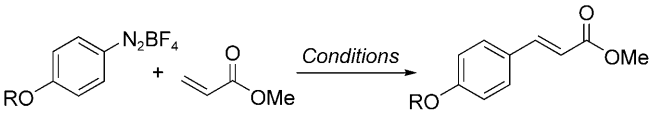
Variable parameters were the solvent, the use of a base, and the choice of precatalyst. Methanol and acetonitrile are common solvents for Mizoroki–Heck reactions, and we decided to use these as typical representatives for a polar protic and a polar aprotic solvent, respectively. We have already briefly commented on the crucial role of a base in Pd-catalyzed transformations using diazonium salts, and it was therefore important to examine transformations under both basic and base-free conditions. For those reactions performed under basic conditions, three equivalents of NaOAc were added. Finally, two different precatalysts were compared. It is known that phosphine ligands are usually detrimental when diazonium salts are used in Mizoroki–Heck reactions,[25] and we therefore used $Pd_2(dba)_3{\cdot}CHCl_3$ as an example for a phosphine-free Pd(0) precatalyst. As a representative Pd(II) precatalyst $Pd(OAc)_2$ was chosen. Thus, 24 different sets of conditions were investigated and the isolated yields of cinnamates **4a–c** are compared in Table 2.

Generally, significantly better yields were obtained in methanol than in acetonitrile for this particular coupling reaction. Under otherwise identical conditions, best yields were observed for the phenoldiazonium salt **1c**, as can be seen from entries 1, 9 and 17. We were particularly surprised by the low yields obtained for the benzyl-protected derivative **1b**, which did not exceed 52% (entry 10). Particularly noteworthy is the effect of a base. From the results summarized in Table 2 it becomes obvious that a detrimental effect of bases in Mizoroki–Heck reactions with arenediazonium salts cannot generally be assumed. While this effect is clearly visible for the *O*-alkylated diazonium salts **1a**, **b** in methanol (entries 1, 2, 5, 6 and 9, 10, 13, 14), the opposite is true in acetonitrile. In this solvent a dramatic improvement was observed upon addition of NaOAc for both **1a** and **1b**, and irrespective of the precatalyst. Very remarkable results were observed for phenoldiazonium salt **1c**. Rather low yields were only obtained in acetonitrile under base-free conditions (entries 20 and 24), while the yields in this solvent in the presence of a base were quantitative. In methanol, the detrimental effect of a base seems to vanish completely, because under these conditions (entries 17 and 21) both catalysts resulted in a quantititative yield of **4c**. Under the normally preferred base-free conditions, yields were slightly lower (entries 18 and 22), but still excellent.

Intrigued by the prospect of a protecting group-free synthesis[51] of phenols and the remarkably high reactivity of **1c** in Mizoroki–Heck reactions, we extended this investigation to other phenoldiazonium salts (Table 3).

To this end, methyl acrylate and various substituted phenoldiazonium salts were coupled in methanol using NaOAc as a base and $Pd(OAc)_2$ as a precatalyst. For comparison, the analogous *O*-methylated arenediazonium salts were also tested under otherwise identical conditions. In Table 3, the isolated yields of the substituted cinnamates **4** obtained from these reactions are compared. As can be seen from entries 1–6, significantly better yields are again obtained for the phenoldiazonium salts **1e**, **g**, **i**, compared to the corresponding methyl ethers **1d**, **f**, **h**. Surprisingly, the coupling reactions of phenoldiazonium salts **1k**, **m** and methyl acrylate (entries 8 and 10) were not successful under the optimized conditions. In both cases, the absence of a base was advantageous and **4k** and **4m** were isolated in 54% and 99% yield, respectively (entries 8 and 10). We could not obtain the diazonium salt **1j**, with a methyl ether and a carboxylate group, however, the coupling product **4j** was accidentally synthesized from **1l** by subsequent ester cleavage. Interestingly, this ester cleavage could be

Table 2. Mizoroki–Heck reactions with methyl acrylate.[a]



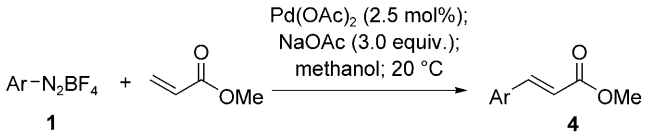
1a (R = Me)
1b (R = Bn)
1c (R = H)

4a (R = Me)
4b (R = Bn)
4c (R = H)

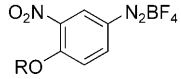
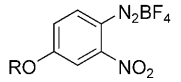
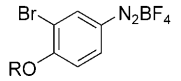
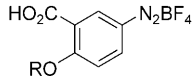
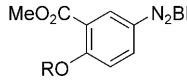
Entry	1	Precatalyst[b]	Solvent	Base[c] (equiv.)	Yield
1	**1a**	$Pd(OAc)_2$	MeOH	(3.0)	72%
2	**1a**	$Pd(OAc)_2$	MeOH	–	83%
3	**1a**	$Pd(OAc)_2$	H_3CCN	(3.0)	52%
4	**1a**	$Pd(OAc)_2$	H_3CCN	–	10%
5	**1a**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	(3.0)	71%
6	**1a**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	–	94%
7	**1a**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	(3.0)	73%
8	**1a**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	–	15%
9	**1b**	$Pd(OAc)_2$	MeOH	(3.0)	32%
10	**1b**	$Pd(OAc)_2$	MeOH	–	52%
11	**1b**	$Pd(OAc)_2$	H_3CCN	(3.0)	15%
12	**1b**	$Pd(OAc)_2$	H_3CCN	–	7%
13	**1b**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	(3.0)	22%
14	**1b**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	–	45%
15	**1b**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	(3.0)	45%
16	**1b**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	–	22%
17	**1c**	$Pd(OAc)_2$	MeOH	(3.0)	99%
18	**1c**	$Pd(OAc)_2$	MeOH	–	95%
19	**1c**	$Pd(OAc)_2$	H_3CCN	(3.0)	99%
20	**1c**	$Pd(OAc)_2$	H_3CCN	–	40%
21	**1c**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	(3.0)	99%
22	**1c**	$Pd_2(dba)_3{\cdot}CHCl_3$	MeOH	–	95%
23	**1c**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	(3.0)	99%
24	**1c**	$Pd_2(dba)_3{\cdot}CHCl_3$	H_3CCN	–	21%

[a] *Reagents and conditions:* **1a**, **1b** or **1c** (1.0 equiv.) and methyl acrylate (2.0 equiv.), appropriate solvent (5.0 mL mmol^{-1}), 20 °C for 12 h.
[b] 2.5 mol% precatalyst were used in all experiments.
[c] The base NaOAc was added prior to the precatalyst.

Table 3. Mizoroki–Heck reactions with other diazonium salts.



1 4

Entry	Ar-N_2BF_4	R (No.)	4	Yield
1		Me (**1d**)	**4d**	0%
2		H (**1e**)	**4e**	80%
3		Me (**1f**)	**4f**	12%[a]
4		H (**1g**)	**4g**	76%[a]
5		Me (**1h**)	**4h**	19%
6		H (**1i**)	**4i**	80%
7		Me (**1j**)	**4j**	–[b]
8		H (**1k**)	**4k**	9%, 54%[c]
9		Me (**1l**)	**4l**	48%,[c,e] 52%[d]
10		H (**1m**)	**4m**	0%, 99%,[c] 94%[d]

[a] Diazonium salts were obtained in solution from the corresponding acetanilides by deacetylation/diazotation and were not isolated.
[b] **4j** was not obtained from **1j**, but by subsequent ester hydrolysis, see entry 9.
[c] Base-free conditions.
[d] Acetonitrile was used instead of methanol.
[e] Reaction proceeds in methanol under ester hydrolysis, resulting in the formation of **4j**.

avoided in acetonitrile and the cinnamate **4l** resulted in 52% yield. For comparison, phenoldiazonium salt **1m** and methyl acrylate were also coupled in acetonitrile, and the yield observed for **4m** was 94% under these conditions. It should be noted that for the reactions of **1l**, **m** in acetonitrile the presence of a base is mandatory, while in methanol base-free conditions are required for these particular diazonium salts.

Mizoroki–Heck Reactions with Other Electron-Deficient Alkenes

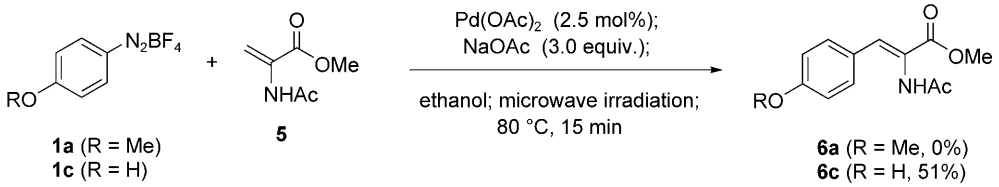
Pd-catalyzed arylation reactions of acetamide **5** have been investigated with a view to the synthesis of acetamidocinnamates **6**, because these compounds are substrates for enantioselective hydrogenation reactions, giving enantiomerically pure amino acids.[52] For instance, derivatives **6a**[53] and **6c**[54] (Scheme 1) were obtained from **5** and the corresponding aryl iodides. To the best of our knowledge, the coupling of **5** with arenediazonium salts has not been investigated so far.

With our standard conditions, neither **1a** nor **1c** reacted with **5** in a defined way. Therefore, ethanol was used as a solvent and the reactions were repeated under reflux. While no coupling product **6a** was obtained from **1a** and **5**, small amounts of **6c** could be isolated when **1c** was used, however, the results were difficult to reproduce which might be attributed to an enhanced rate of decomposition upon heating. Eventually, a successful coupling of **1c** and **5** to **6c** was achieved by conducting the reaction in ethanol under microwave irradiation at 80 °C for 15 min. While **1a** was still unreactive under these conditions, we could isolate **6c** in a fair yield of 51% (Scheme 1).

A striking difference in reactivity was also observed for acrylic amide **7**. This substrate was chosen because the products resulting from a Mizoroki–Heck reaction, the cinnamic amides **8**, have recently attracted some attention as antagonists of certain ion channels.[55,56] Similar to substrate **5**, the reaction fails completely with the methoxy-substituted diazonium salts **1a** and **1d**, whereas yields of 91% and 88%, respectively, were achieved with phenoldiazonium salts **1c** and **1e** (Table 4).

Phenoldiazonium Salts or Quinone Diazides?

Currently, we are unable to provide a fully conclusive explanation for the enhanced reactivity of phenoldiazonium salts in Mizoroki–Heck reactions documented in this study. However, an analysis of the reaction mixtures of those experiments where the coupling product was obtained in poor yield or not at all revealed that hydrodediazonation appears to be a major problem for less reactive diazonium salts under our conditions. This becomes particularly clear for attempted Mizoroki–Heck reactions with diazonium salt **1d** (see Table 3, entry 1 and Table 4, entry 3). In both cases, *ortho*-nitroanisole was isolated in quantitative yield. We assume that the superior reactivity of phenoldiazonium salts originates from a higher stability towards competing reduction and that the forma-



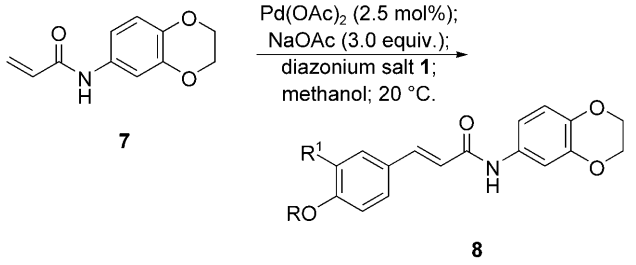
1a (R = Me)
1c (R = H)

5

6a (R = Me, 0%)
6c (R = H, 51%)

Scheme 1. Synthesis of acetamidocinnamate **6c**.

Table 4. Mizoroki–Heck reactions with acrylic amide **7**.



7 **8**

Entry	**1**	R	R^1	**8**	Yield
1	**1a**	Me	H	**8a**	0%
2	**1c**	H	H	**8c**	91%
3	**1d**	Me	NO_2	**8d**	0%
4	**1e**	H	NO_2	**8e**	88%

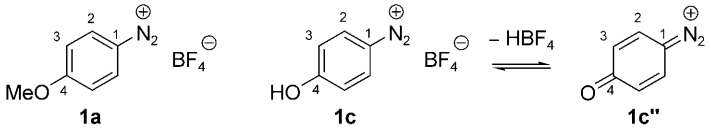
tion of quinone diazides[43] is one reason for this improved stability. In order to check if a quinone diazide structure such as **1c″** is of any relevance under the conditions of Mizoroki–Heck reactions, ^{13}C NMR spectra were recorded in CD_3OD and CD_3CN in the presence or absence of the base NaOAc. For comparison, spectra for methoxybenzenediazonium salt **1a** were obtained under identical conditions. The data are compiled in Table 5. We observed very similar chemical shift values for **1a** and **1c** in DMSO. In the case of **1a** a quinone diazide structure is not possible, and the chemical shift values are affected only to a small extent by the solvent and the presence of a base. In contrast, significantly more pronounced solvent effects were observed in methanol and in acetonitrile for **1c**. Particularly large $\Delta\delta$ values are found for carbon atoms C-1 and C-4. While the $\delta(^{13}C)$ values for **1c** in DMSO are in accord with a diazonium cation structure (entry 6), the values recorded in methanol or in acetonitrile in the presence of NaOAc (entries 8 and 10) are both indicative for a quinone diazide structure **1c″**. The chemical shift values observed in these solvents in the absence of a base (entries 7 and 9) cannot be assigned to either of these species but are obviously average values, resulting from a proton exchange which is rapid on the NMR time-scale. While these observations are indicative for a significant contribution of the quinone diazide structure under Mizoroki–Heck conditions, they do not provide an explanation for the rather low yields observed under base-free conditions in acetonitrile (Table 2, entries 20 and 24). Obviously, other effects such as catalyst-solvent interaction,[17] play a more important role in these cases.

A One-Flask Synthesis of the Heterocyclic Fragment of Aripiprazole

Aripiprazole (**10**) is an atypical neuroleptic (antipsychotic) drug[57] that does not only act as a dopamine D_2-antagonist but also as a partial autoreceptor agonist.[58] It has been reported that aripiprazole affects both positive and negative symptoms of schizophrenia.[57] A synthesis of aripiprazole (**10**) by *O*-alkylation of the heterocyclic key fragment **9** has been reported by Oshiro et al.[58] Dihydroquinolone **9** is in turn available from *meta*-anisidine using aromatic substitution reactions and demethylation reactions with strong Lewis acids.[59] An alternative synthesis of **9** was very recently devised while our work[38] was in progress. Felpin et al. started from a benzyl-protected diazonium salt which was converted to **9** using the Heck–reduction–cyclization–debenzylation (HRCD) sequence developed in their group.[23]

We pursued a strategy that uses the acetanilide **2g** as a starting material. Conversion of **2g** to a phenoldiazonium salt **1g** was achieved in methanol using the

Table 5. ^{13}C NMR data for **1a** and **1c**.



1a **1c** **1c"**

Entry	**1**	Solvent	NaOAc (equiv.)	δ (C-1) [ppm]	δ (C-2) [ppm]	δ (C-3) [ppm]	δ (C-4) [ppm]
1	**1a**	DMSO-d_6	–	103.3	136.1	117.3	168.8
2	**1a**	CD_3OD	–	103.7	137.3	118.9	171.7
3	**1a**	CD_3OD	3.0	103.7	137.3	118.9	171.6
4	**1a**	CD_3CN	–	102.8	138.9	119.0	171.4
5	**1a**	CD_3CN	3.0	102.8	136.8	118.9	171.3
6	**1c**	DMSO-d_6	–	99.7	136.5	118.8	169.5
7	**1c**	CD_3OD	–	92.7	136.4	122.4	176.9
8	**1c**	CD_3OD	3.0	80.9	134.7	125.6	184.1
9	**1c**	CD_3CN	–	90.6	135.9	122.7	177.5
10	**1c**	CD_3CN	3.0	77.5	132.6	125.3	182.2

deacetylation–diazotation sequence as outlined above. As methanol is also the ideal solvent for a subsequent Mizoroki–Heck coupling with methyl acrylate, we investigated the possibility to conduct the Pd-catalyzed steps without isolating the diazonium salt, simply by adding methyl acrylate, the base NaOAc, and a catalytic amount of $Pd(OAc)_2$ to the reaction mixture, followed by addition of activated charcoal and hydrogen. This one-flask sequence comprises six steps, including the final spontaneous lactam formation, and proceeds in 73% overall yield based on **2g**. Operational benefits of this sequence are the crystallinity and air-stability of the starting acetanilide, and the possibility to conduct the entire sequence without removal or exchange of any solvents, simply by adding the appropriate reagents and catalysts in due course (Scheme 2).

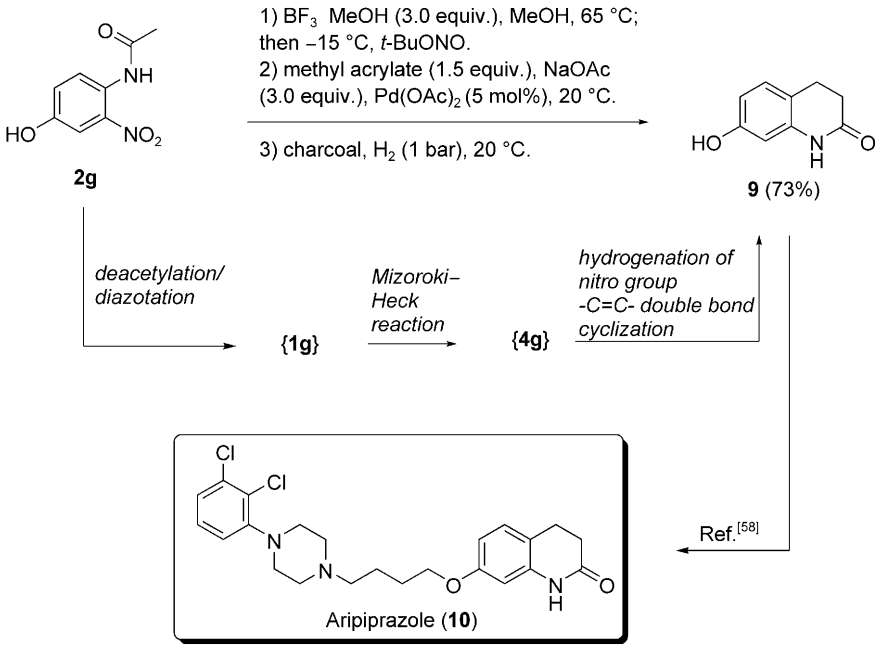
Conclusions

In conclusion, we have shown that 4-phenoldiazonium salts are useful arylating reagents in Pd-catalyzed protecting group-free syntheses of phenols. Surprisingly, the reactivity of these reagents is in most cases significantly higher than for the analogous *O*-alkylarenediazonium salts. Based on NMR-spectroscopic investigations we propose that quinone diazide structures are involved under the conditions commonly used for Mizoroki–Heck reactions. Furthermore, we showed that 4-phenoldiazonium salts are advantageously synthesized from acetanilides using the deacetylation–diazotation sequence, and that this sequence may be extended by Pd-catalyzed transformations. We could illustrate the synthetic potential for a one-flask synthesis of a key fragment in the synthesis of the neuroleptic aripiprazole. Further work directed at the application of phenoldiazonium salts in transition metal-catalyzed reactions is currently underway in our laboratory.

Experimental Section

General Remarks

All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz or 500 MHz in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz or at 125 MHz in $CDCl_3$ with $CDCl_3$ ($\delta = 77.0$ ppm) as an internal standard. Whenever the solubility of the sample was insufficient in $CDCl_3$, one of the following solvents was used for NMR measurements: DMSO-d_6 (DMSO-d_5 as internal standard for ^{1}H NMR spectroscopy, $\delta = 2.50$ ppm, DMSO-d_6 as internal standard for ^{13}C NMR spectroscopy, $\delta = 39.5$ ppm); methanol-d_4 (CD_2HOD as internal standard for ^{1}H NMR spectroscopy, $\delta = 3.31$ ppm, CD_3OD as internal standard for ^{13}C NMR spectroscopy, $\delta = 49.2$ ppm); acetone-d_6 [$CD_2HC(O)CD_3$ as internal standard for ^{1}H NMR spectroscopy, $\delta = 2.05$ ppm, $CD_3C(O)CD_3$ as internal standard for ^{13}C NMR spectroscopy, $\delta = 29.9$ ppm]; acetonitrile-d_3 (CD_2HCN as internal standard for ^{1}H NMR spectroscopy, $\delta = 1.39$ ppm, CD_3CN as internal standard for ^{13}C NMR



Scheme 2. One-flask sequence for the synthesis of the aripiprazole key fragment **9**.

spectroscopy, $\delta = 1.4$ ppm). The number of coupled protons was analyzed by DEPT or APT experiments and is denoted by a number in parantheses following the chemical shift value. Whenever NMR peak assignments in the ^{13}C NMR spectra are given, these are based on H,H- and H,C-correlation spectroscopy. IR spectra were recorded as films on NaCl or as KBr discs. The peak intensities are defined as strong (s), medium (m) or weak (w). Mass spectra were obtained at 70 eV. Reactions under microwave irradiation were conducted in a commercial microwave reactor for laboratory purposes (CEM-Discover).

Synthesis of Phenoldiazonium Salts 1

4-Hydroxybenzenediazonium tetrafluoroborate (1c): A suspension of 4-acetamidophenol (5.0 g, 33 mmol) in HBF_4 (15 mL, 3.6 M solution in water) and 2-propanol (5 mL) was heated at 90 °C for 3 h until a clear solution resulted, indicating complete consumption of the starting material. This solution was cooled to 0 °C and $NaNO_2$ (3.1 g, 44 mmol) was added slowly. The resulting suspension was stirred for 30 min at 0 °C. The solid was filtered through a Büchner funnel and washed with cold diethyl ether (100 mL). Product **1c** was obtained as a yellow solid: yield: 4.93 g (24 mmol, 72%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 8.49$ (d, $J = 9.3$ Hz, 2H), 7.19 (d, $J = 9.3$ Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 169.5$ (0), 136.5 (1), 118.8 (1), 99.7 (0); IR (KBr disc): $\tilde{\nu} = 3108$ (w), 2238 (m, N_2), 1563 (s), 1379 (s), 1294 (s), 1086 (s), 1041 cm^{-1} (s); MS (ESI): $m/z = 135$ (M^+, 100); HR-MS (ESI): $m/z = 121.0394$, calcd. for $C_6H_5N_2O$ $[M]^+$: 121.0402.

4-Hydroxy-3-nitrobenzenediazonium tetrafluoroborate (1e): A solution of **2e** (590 mg, 3.0 mmol) and boron trifluoride·methanol (9.1 mmol, 0.98 mL) in anhydrous MeOH (5 mL) was heated under reflux until full conversion of the acetamide. The solution was then cooled to −15 °C and treated with *tert*-butyl nitrite (0.54 mL, 4.5 mmol). The diazonium salt precipitated within 15 min. The suspension was stirred for another hour, filtered and the solid was washed with cold ethanol (20 mL) and MTBE (20 mL). Product **1e** was obtained as a yellow solid: yield: 592 mg (2.40 mmol, 78%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 9.68$ [s (br), 1H], 8.92 (d, $J = 2.9$ Hz, 1H), 7.86 (dd, $J = 9.8$, 2.9 Hz, 1H), 6.52 (d, $J = 9.8$, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 170.1$, 140.4, 133.6, 131.6, 128.1, 80.4; IR (neat): $\tilde{\nu} = 3081$ (m), 2166 (s, N_2), 1597 (s), 1499 cm^{-1} (s); MS (ESI): $m/z = 166$ ($[M]^+$, 100), 138 (4), 99 (15); HR-MS (ESI): $m/z = 166.0263$, calcd. for $C_6H_4N_3O_3$ $[M]^+$: 166.0253.

3-Bromo-4-hydroxybenzenediazonium tetrafluoroborate (1i): Following the procedure for **1e**, the title compound **1i** was obtained from **2i** (690 mg, 3.0 mmol) as a colourless solid; yield: 695 mg (2.43 mmol, 80%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 11.65$ (s, 1H), 8.74 (d, $J = 2.6$ Hz, 1H), 8.31 (dd, $J = 9.3$, 2.6 Hz, 1H), 7.05 (d, $J = 9.3$, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 168.8$, 136.5, 134.4, 119.4, 112.8, 94.4; IR (neat): $\tilde{\nu} = 3145$ (m), 2235 (s, N_2), 1552 (s), 1424 cm^{-1} (s); MS (ESI): $m/z = 199$ ($[M]^+$, 100), 171 (12), 99 (18); HR-MS (ESI): $m/z = 198.9521$, calcd. for $C_6H_4N_2OBr$ $[M]^+$: 198.9507.

3-Carboxy-4-hydroxybenzenediazonium tetrafluoroborate (1k): A suspension of **3k** (10.0 g, 65 mmol), HBF_4 (3.6 M solution in water, 30 mL) and 2-propanol (10 mL) was stirred for 30 min at ambient temperature. The reaction mixture was cooled to 0 °C and $NaNO_2$ (9.0 g, 130 mmol) was added slowly. The resulting suspension was stirred for 30 min at 0 °C. The solid was filtered through a Büchner funnel and washed with cold water (250 mL), ethanol (250 mL) and diethyl ether (250 mL). Product **1k** was obtained as a beige solid; yield: 11.4 g (45 mmol, 70%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 8.89$ (d, $J = 2.9$ Hz, 1H), 8.11 (dd, $J = 9.5$, 2.9 Hz, 1H), 6.73 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 180.2$ (0), 165.8 (0), 138.9 (1), 134.9 (1), 124.0 (1), 119.5 (0), 87.2 (0); IR (neat): $\tilde{\nu} = 3226$ (w), 3102 (w), 2180 (s), 1708 (s), 1682 (m), 1655 (m), 1596 (s), 1596 (s), 1477 (s), 1369 (m), 1128 cm^{-1} (s); MS (ESI): $m/z = 165$ (M^+, 20), 147 (40), 121 (100); HR-MS (ESI): $m/z = 165.0302$, calcd. for $C_7H_5N_2O_3$ $[M]^+$: 165.0300.

4-Methoxy-3-(methoxycarbonyl)benzenediazonium tetrafluoroborate (1l): Following the procedure for **1k**, the title compound **1l** was obtained from **3l** (3.0 g, 17 mmol) as a beige solid; yield: 3.3 g (12 mmol, 71%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 9.04$ (d, $J = 2.6$ Hz, 1H), 8.79 (dd, $J = 9.5$, 2.7 Hz, 1H), 7.73 (d, $J = 9.5$ Hz, 1H), 4.13 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 167.0$ (0), 162.6 (0), 138.7 (1), 136.9 (1), 121.8 (0), 116.1 (1), 104.1 (0), 58.4 (3), 53.0 (3); IR (KBr disc): $\tilde{\nu} = 3122$ (m), 3009 (m), 2962 (m), 2263 (s, N_2), 1733 (s), 1702 (s), 1584 (s), 1562 (s), 1490 (s), 1465 (m), 1428 (s), 1350 (m), 1310 (s), 1245 cm^{-1} (s); MS (ESI): $m/z = 193$ (M^+, 100); HR-MS (ESI): $m/z = 193.0623$, calcd. for $C_9H_9N_2O_3$ $[M]^+$: 193.0613.

4-Hydroxy-3-(methoxycarbonyl)benzenediazonium tetrafluoroborate (1m): Following the procedure for **1k**, the title compound **1m** was obtained from **3m** (3.0 g, 18 mmol) as a colourless solid; yield: 4.5 g (17 mmol, 94%). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 9.05$ (d, $J = 2.7$ Hz, 1H), 8.53 (dd, $J = 9.3$, 2.7 Hz, 1H), 7.35 (d, $J = 9.3$ Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 168.8$ (0), 163.7 (0), 138.7 (1), 137.3 (1), 121.1 (1), 119.6 (0), 100.3 (0), 52.9 (3); IR (KBrdisc): $\tilde{\nu} = 3115$ (m), 3098 (m), 2267 (s, N_2), 1687 (s), 1597 (s), 1567 (s), 1476 (s), 1354 (s), 1315 (s), 1273 (s), 1214 cm^{-1} (s); MS (ESI): $m/z = 179$ (M^+, 100); HR-MS (ESI): $m/z = 179.0458$, calcd. for $C_8H_7N_2O_3$ $[M]^+$: 179.0457.

General Procedure for Mizoroki–Heck Reactions with Isolated Diazonium Salts

To a suspension of the corresponding arenediazonium salt **1** (0.5 mmol), methyl acrylate (1.0 mmol) and NaOAc (1.5 mmol) in anhydrous and degassed methanol or acetonitrile (5 mL) was added the appropriate precatalyst (2.5 mol%) at room temperature. The reaction mixture was stirred for 12 h. After this time, it was treated with active charcoal (50 mg) and concentrated under reduced pressure. The charcoal residue was extracted with ethyl acetate (25 mL) in an ultrasonic bath for 5 min, filtered over celite and evaporated. The residue was purified by column chromatography on silica. Base-free coupling reactions were conducted without adding NaOAc under otherwise identical conditions.

***(E)*-Methyl 3-(4-methoxyphenyl)acrylate (4a):** Product **4a** was obtained under base-free conditions as a colourless solid; yield: 80 mg (83%); mp 88–91 °C (reported in the literature:[60] 88–89 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 16.0$ Hz, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J =$

8.8 Hz, 2H), 6.30 (d, $J=16.0$ Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.6$ (0), 161.3 (0), 144.4 (1), 129.6 (1), 127.1 (0), 115.2 (1), 114.3 (1), 55.3 (3), 51.5 (3); IR (KBr disc): $\tilde{\nu}=2949$ (m), 1716 (s), 1637 (s), 1601 (s), 1511 (s), 1432 (s), 1329 (s), 1301 (s), 1287 (s), 1255 cm^{-1} (s); MS (ESI): $m/z=193$ ($[M+H]^+$, 44), 161 (100), 147 (25); HR-MS (ESI): $m/z=193.0870$, calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.0865; anal. calcd. for $C_{11}H_{12}O_3$: C 68.7, H 6.3; found: C 68.6, H 6.3.

(*E*)-Methyl 3-[4-(benzyloxy)pheny])acrylate (4b): Product **4b** was obtained under base-free conditions as a colourless solid; yield: 71 mg (52%); mp 134–136 °C (reported in the literature:[61] 136 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.65$ (d, $J=16.0$ Hz, 1H), 7.47 (d, $J=8.7$ Hz, 2H), 7.45–7.30 (5H), 6.98 (d, $J=8.8$ Hz, 2H), 6.32 (d, $J=16.0$ Hz, 1H), 5.10 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.7$ (0), 160.5 (0), 144.4 (1), 136.5 (0), 129.7 (1), 128.6 (1), 128.1 (1), 127.4 (1), 127.4 (0), 115.4 (1), 115.2 (1), 70.1 (2), 51.5 (3); IR (KBr disc): $\tilde{\nu}=2948$ (w), 1717 (s), 1634 (m), 1602 (m), 1510 (s), 1285 (s), 1250 (m), 1203 (m), 1170 cm^{-1} (s); MS (EI): $m/z=268$ ($[M]^+$, 48), 218 (54), 91 (100); HR-MS (EI): $m/z=268.1092$, calcd. for $C_{17}H_{16}O_3$ $[M]^+$: 268.1099; anal. calcd. for $C_{17}H_{16}O_3$: C 76.1, H 6.0; found: C 76.0, H 5.8.

(*E*)-Methyl 3-(4-hydroxyphenyl)acrylate (4c): Product **4c** was obtained in either methanol or acetonitrile under basic conditions as a colourless solid; yield: 89 mg (99%); mp 134–136 °C (reported in the literature:[62] 135–137 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.64$ (d, $J=16.0$ Hz, 1H), 7.42 (d, $J=8.5$ Hz, 2H), 6.86 (d, $J=8.6$ Hz, 2H), 6.30 (d, $J=16.0$ Hz, 1H), 6.06 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.2$ (0), 158.0 (0), 144.9 (1), 130.0 (1), 127.0 (0), 115.9 (1), 115.0 (1), 51.7 (3); IR (neat): $\tilde{\nu}=3472$ (s), 1687 (s), 1432 (s), 1176 (s), 984 cm^{-1} (s); MS (ESI): $m/z=179$ ($[M+H]^+$, 100), 147 (28), 116 (30); HR-MS (ESI): $m/z=179.0724$, calcd. for $C_{10}H_{11}O_3$ $[M+H]^+$: 179.0708; anal. calcd. for $C_{10}H_{10}O_3$: C 67.4, H 5.7; found: C 67.4, H 5.5.

(*E*)-Methyl 3-(4-hydroxy-3-nitrophenyl)acrylate (4e): Product **4e** was obtained as a colourless solid; yield: 89 mg (0.40 mmol, 80%); mp 144 °C (reported in the literature:[63] 142–148 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.70$ (s, 1H), 8.23 (d, $J=2.2$ Hz, 1H), 7.75 (dd, $J=8.8$, 2.2 Hz, 1H), 7.61 (d, $J=16.0$ Hz, 1H), 7.19 (d, $J=8.8$ Hz, 1H), 6.39 (d, $J=16.0$ Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.0$, 156.3, 141.8, 136.1, 133.9, 127.5, 125.1, 121.0, 119.0, 52.1; IR (KBr disc): $\tilde{\nu}=3262$ (m), 2924 (m), 1724 (s), 1620 (s), 1533 cm^{-1} (s); MS (ESI): $m/z=223$ ($[M]^+$, 85), 192 (100), 146 (28); HR-MS (ESI): $m/z=223.0491$, calcd. for $C_{10}H_9NO_5$ $[M]^+$: 223.0481; anal. calcd. for $C_{10}H_9NO_5$: C 53.8, H 4.1, N 6.3; found: C 54.2, H 4.2, N, 6.2.

(*E*)-Methyl 3-(3-bromo-4-methoxyphenyl)acrylate (4h): Product **4h** was obtained as a colourless solid; yield: 27 mg (0.10 mmol, 19%); mp 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.72$ (d, $J=2.1$ Hz, 1H), 7.55 (d, $J=16.0$ Hz, 1H), 7.41 (dd, $J=8.5$, 2.1 Hz, 1H), 6.87 (d, $J=8.6$ Hz, 1H), 6.29 (d, $J=16.0$ Hz, 1H), 3.90 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.5$, 157.6, 143.2, 132.8, 129.1, 128.7, 116.9, 112.5, 112.0, 56.6, 51.9. IR (KBr disc): $\tilde{\nu}=3438$ (m), 1704 (s), 1633 (s), 1497 (s), 1265 cm^{-1} (s); MS (ESI): $m/z=271$ ($[M+H]^+$, 15), 239 (100), 160 (68); HR-MS (ESI): $m/z=270.9984$, calcd. for $C_{11}H_{12}O_3Br$ $[M+H]^+$: 270.9970; anal. calcd. for $C_{11}H_{11}O_3Br$: C 48.7, H 4.1; found: C 48.6, H 3.9.

(*E*)-Methyl 3-(3-bromo-4-hydroxyphenyl)acrylate (4i): Product **4i** was obtained as a colourless solid; yield: 102 mg (0.40 mmol, 80%); mp 109–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.63$ (d, $J=2.0$ Hz, 1H), 7.54 (d, $J=16.0$ Hz, 1H), 7.38 (dd, $J=8.5$, 2.0 Hz, 1H), 7.00 (d, $J=8.5$ Hz, 1H), 6.28 (d, $J=16.0$ Hz, 1H), 5.86 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.6$, 154.2, 143.2, 132.0, 129.3, 128.9, 117.0, 116.7, 111.0, 51.9; IR (KBr): $\tilde{\nu}=3312$ (m), 1688 (s), 1631 (s), 1600 (s), 1430 cm^{-1} (s); MS (ESI): $m/z=257$ ($[M+H]^+$, 16), 225 (100), 146 (41); HR-MS (ESI); $m/z=256.9813$, calcd. for $C_{10}H_{10}O_3Br$ $[M+H]^+$: 256.9807; anal. calcd. for $C_{10}H_9O_3Br$: C 46.7, H 3.5; found: C 46.6, H 3.4.

(*E*)-2-Methoxy-5-(3-methoxy-3-oxoprop-1-enyl)benzoic acid (4j): Product. **4j** was obtained from **1l** under base-free conditions with concomitant ester hydrolysis as a colourless solid; yield: 56 mg (0.24 mmol, 48%); mp 139–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.34$ (d, $J=2.3$ Hz, 1H), 7.72 (dd, $J=8.6$, 2.3 Hz, 1H), 7.65 (d, $J=16.1$ Hz, 1H), 7.10 (d, $J=8.7$ Hz, 1H), 6.43 (d, $J=16.0$ Hz, 1H), 4.11 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.1$, 159.3, 142.6, 134.3, 133.2, 128.5, 118.0, 112.3, 56.9, 51.7; IR (neat): $\tilde{\nu}=2952$ (w), 1712 (s), 1606 (m), 1264 cm^{-1} (s); MS (ESI): $m/z=237$ ($[M+H]^+$, 30); 219 (100); HR-MS (ESI): $m/z=237.0751$, calcd. for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0763.

(*E*)-2-Hydroxy-5-(3-methoxy-3-oxoprop-1-enyl)benzoic acid (4k): Product **4k** was obtained under base-free conditions as a colourless solid; yield: 60 mg (0.27 mmol, 54%); mp 213–214 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=8.06$ (s, 1H), 7.93 (d, $J=8.7$ Hz, 1H), 7.64 (d, $J=16.0$ Hz, 1H), 7.00 (d, $J=8.7$ Hz, 1H), 6.51 (d, $J=16.0$ Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=171.4$ (0), 166.7 (0), 162.6 (0), 143.5 (1), 134.5 (1), 131.3 (1), 125.4 (1), 117.9 (1), 116.0 (1), 113.5 (0), 51.3 (3); IR (KBr disc): $\tilde{\nu}=2966$ (m), 2855 (m), 1631 (s), 1594 (s), 1491 (s), 1432 (s), 1369 (m), 1339 (s), 1301 (s), 1263 (s), 1204 cm^{-1} (s); MS (ESI): $m/z=223$ ($[M+H]^+$, 90); 205 (100); HR-MS (ESI): $m/z=223.0622$, calcd. for $C_{11}H_{11}O_5$ $[M+H]^+$: 223.0606; anal. calcd. for $C_{11}H_{10}O_5$: C 59.5, H 4.5; found: C 59.2, H 4.4.

(*E*)-Methyl 2-methoxy-5-(3-methoxy-3-oxoprop-1-enyl)-benzoate (4l): Product **4l** was obtained in acetonitrile as a colourless solid; yield: 65 mg (0.26 mmol, 52%); mp 87–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.90$ (d, $J=2.3$ Hz, 1H), 7.56 (d, $J=16.0$ Hz, 1H), 7.55 (dd, $J=8.5$, 2.1 Hz, 1H), 6.92 (d, $J=8.8$ Hz, 1H), 6.29 (d, $J=16.0$ Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.1$, 165.7, 160.3, 143.1, 132.9, 131.3, 126.4, 120.3, 116.5, 112.2, 56.0, 52.0, 51.4; IR (neat): $\tilde{\nu}=2950$ (w), 1704 (s), 1605 (m), 1434 (m), 1260 (s), 1166 cm^{-1} (s); MS (ESI): $m/z=251$ ($[M+H]^+$, 47); 219 (100); HR-MS (ESI): $m/z=251.0899$, calcd. for $C_{13}H_{15}O_5$ $[M+H]^+$: 251.0919; anal. calcd. for $C_{13}H_{14}O_5$: C 62.4, H 5.6; found: C 62.3, H 5.5.

(*E*)-Methyl 2-hydroxy-5-(3-methoxy-3-oxoprop-1-enyl)-benzoate (4m): Product **4m** was obtained under base-free conditions as a colourless solid; yield: 118 mg (0.5 mmol, 99%); mp 94–96 °C (reported in the literature:[64] 92–94 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.94$ (s, 1H), 7.94 (d, $J=2.0$ Hz, 1H), 7.59 (dd, $J=8.6$, 2.2 Hz, 1H), 7.57 (d, $J=16.0$ Hz, 1H), 6.95 (d, $J=8.7$ Hz, 1H), 6.29 (d, $J=16.0$ Hz, 1H), 3.94 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):

δ = 170.0 (0), 167.3 (0), 163.0 (0), 143.4 (1), 134.4 (1), 130.3 (1), 125.8 (0), 118.3 (1), 116.2 (1), 112.5 (0), 52.5 (3), 51.5 (3); IR (neat): $\tilde{\nu}$ = 3155 (w), 2953 (w), 1712 (m), 1675 (s), 1635 (s), 1608 (m), 1592 (m), 1491 (m), 1440 (s), 1352 (m), 1308 (m), 1287 (m), 1203 (s), 1167 cm^{-1} (s); MS (ESI): *m/z* = 227 ($[M+H]^+$, 18); 205 (100); HR-MS (ESI): *m/z* = 237.0766, calcd. for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0763; anal. calcd. for $C_{12}H_{12}O_5$: C 61.0, H 5.1; found: C 60.9, H 4.9.

One-Flask Deacetylation–Diazotation and Mizoroki–Heck Reaction with Methyl Acrylate

(*E*)-Methyl 3-(4-methoxy-2-nitrophenyl)acrylate (4f): To a solution of **2f** (636 mg, 3.03 mmol) in anhydrous MeOH (5 mL) was added BF_3·MeOH (0.98 mL, 9.08 mmol). The solution was stirred for 5 h under reflux and subsequently cooled to −15 °C. After addition of *tert*-butyl nitrite (0.54 mL, 4.54 mmol) the solution was stirred for 20 min while raising the temperature to 0 °C. To this solution was added NaOAc (745 mg, 9.08 mmol) and a colourless solid started to precipitate. The suspension was dissolved by addition of anhydrous MeOH (5 mL). Methyl acrylate (0.41 mL, 4.54 mmol) and $Pd(OAc)_2$ (34 mg, 5 mol%) were then added. The solution was stirred for 12 h at ambient temperature. The reaction was quenched with hydrochloric acid (1 M, 20 mL) and extracted with MTBE (60 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica, *n*-hexane:MTBE 1:2) to give **4f** as an orange solid; yield: 85 mg (0.36 mmol, 12%); mp 90 °C (reported in the literature:[65] 91–92 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 15.8 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.16 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.6 (0), 161.0 (0), 149.5 (0), 139.6 (1), 130.0 (1), 122.6 (0), 121.2 (1), 120.0 (1), 109.6 (1), 56.1 (3), 52.0 (3); IR (KBr disk): $\tilde{\nu}$ = 3294 (w), 2959 (w), 1718 (s), 1524 (s), 1349 (s), 1280 cm^{-1} (s); MS (ESI): *m/z* = 238 ($[M+H]^+$, 10), 206 (80), 160 (100); HR-MS (ESI): *m/z* = 238.0694, calcd. for $C_{11}H_{12}NO_5$ $[M+H]^+$: 238.0715; anal. calcd. for $C_{11}H_{11}NO_5$: C 55.7, H 4.7, N 5.9; found: C 55.6, H 4.3, N 5.9.

(*E*)-Methyl 3-(4-hydroxy-2-nitrophenyl)acrylate (4g): Following the procedure for **4f**, **4g** was obtained from **2g** (594 mg, 3.03 mmol) as an orange solid; yield: 510 mg (2.30 mmol, 76%): mp 202–207 °C. ^{1}H NMR (300 MHz, methanol-d_4): δ = 7.93 (d, *J* = 15.8 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, methanol-d_4): δ = 168.7, 161.3, 151.5, 141.0, 131.3, 121.8, 121.6, 120.8, 112.2, 52.4; IR (KBr disc): $\tilde{\nu}$ = 3114 (m), 1656 (s), 1400 (s), 1199 cm^{-1} (s); MS (ESI): *m/z* = 224 (21), 192 (100), 146 (41); HR-MS (ESI): *m/z* = 224.0565, calcd. for $C_{10}H_{10}NO_5$ $[M+H]^+$: 224.0559; anal. calcd. for $C_{10}H_9NO_5$: C 53.8, H 4.1, N 6.3; found: C 53.8, H 4.0, N 6.2.

Mizoroki–Heck Reactions with Alkenes 5 and 7

(*Z*)-Methyl 2-acetamido-3-(4-hydroxyphenyl)acrylate (6c): To a suspension of **1c** (208 mg, 1.00 mmol), **5** (143 mg, 1.0 mmol) and NaOAc (246 mg, 3.0 mmol) in anhydrous ethanol (5 mL) in a sealable tube was added $Pd(OAc)_2$ (6 mg, 2.5 mol%). The tube was sealed and heated under microwave irradiation (CEM-Discover) to 80 °C for 15 min. After cooling to ambient temperature, the mixture was treated with active charcoal (100 mg) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (50 mL) in an ultrasonic bath for 5 min, filtered through celite and evaporated. The residue was purified by column chromatography (silica, ethyl acetate : MTBE 2:1) to afford **6c** as a colourless solid; yield: 120 mg (0.51 mmol, 51%); mp 171–173 °C. ^{1}H NMR (300 MHz, methanol-d_4): δ = 7.48 (d, *J* = 8.6 Hz, 2H), 7.40 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, methanol-d_4): δ = 173.5 (0), 167.7 (0), 160.7 (0), 136.7 (0), 133.3 (1), 126.1 (1), 123.4 (0), 116.8 (1), 53.0 (3), 22.7 (3); IR (KBr disc): $\tilde{\nu}$ = 3238 (s), 2378 (w), 1715 (s), 1635 (s), 1599 (s), 1542 (s), 1509 (s), 1468 (m), 1432 (s), 1370 (s), 1312 (s), 1272 (s), 1232 (s), 1201 (s) 1172 (s), 1129 cm^{-1} (m); MS (ESI): *m/z* = 236 ($[M+H]^+$, 20), 204 (100); HR-MS (ESI): *m/z* = 236.0924, calcd. for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923; anal. calcd. for $C_{12}H_{13}NO_4$: C 61.3, H 5.6, N 6.0; found: C 61.0, H 5.3, N 5.9.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-hydroxyphenyl)acrylamide (8c): To a suspension of **7** (205 mg, 1.00 mmol), **1c** (208 mg, 1.00 mmol) and NaOAc (246 mg, 3.00 mmol) in anhydrous MeOH (10 mL) was added $Pd(OAc)_2$ (2.5 mol%, 6 mg) at ambient temperature. The reaction mixture was stirred for 12 h and then treated with active charcoal (100 mg) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (100 mL) in an ultrasonic bath for 5 min, filtered through celite and evaporated. The residue was purified by column chromatography (silica, ethyl acetate:MTBE 1:1). Product **8c** was obtained as a colourless solid; yield: 270 mg (0.91 mmol, 91%); mp 206–208 °C (reported in the literature:[55] 205 °C-207 °C). ^{1}H NMR (300 MHz, methanol-d_4): δ = 7.55 (d, *J* = 15.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 15.6 Hz, 1H), 4.26–4.18 (4H); ^{13}C NMR (75 MHz, methanol-d_4): δ = 167.2 (0), 160.9 (0), 144.9 (0), 142.8 (0), 141.9 (0), 133.9 (0), 130.8 (1), 127.9 (1), 118.9 (1), 118.1 (1), 116.9 (1), 114.7 (1), 110.8 (1), 65.9 (2), 65.7 (2); IR (neat): $\tilde{\nu}$ = 3290 (m), 1655 (m), 1602 (s), 1505 (s), 1431 (m), 1302 (m), 1275 (m), 1241 (m), 1211 (s), 1170 (m), 1121 (w), 1066 cm^{-1} (m); MS (ESI): *m/z* = 298 ($[M+H]^+$, 100); HR-MS (ESI): *m/z* = 298.1058, calcd. for $C_{17}H_{16}NO_4$ $[M+H]^+$: 298.1079; anal. calcd. for $C_{17}H_{15}NO_4$: C 68.7, H 5.1, N 4.7; found: C 68.2, H 5.0, N 4.6.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-hydroxy-3-nitrophenyl)acrylamide (8e): Following the procedure for **8c**, **8e** was obtained from **7** (205 mg, 1.00 mmol) and **1e** (208 mg, 1.00 mmol) as a red solid; yield: 300 mg (0.88 mmol, 88%); mp 206–208 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.42 (s, 1H), 10.01 (s, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.52 (d, *J* = 15.7 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 15.7 Hz, 1H), 4.28–4.18 (4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.8 (0), 153.7 (0), 143.8, 140.3, 138.4, 138.0, 134.6, 133.8, 127.2, 125.2, 122.8, 120.5, 117.7, 113.2, 109.1, 65.0 (2), 64.8 (2); IR (KBr disc): $\tilde{\nu}$ = 3440 (s), 1661 (m), 1620 (s), 1534 (s), 1506 (s), 1456 (w), 1425 (m), 1328 (m), 1281 (s), 1255 (m), 1207 (s), 1125 (w), 1065 cm^{-1} (m); MS (ESI): *m/z* = 343 ($[M+H]^+$, 100); HR-MS (ESI):

$m/z = 365.0765$, calcd. for $C_{17}H_{14}N_2O_6Na$ $[M+Na]^+$: 365.0750.

Synthesis of the Key Fragment of Aripiprazole

7-Hydroxy-3,4-dihydroquinolin-2(1*H*)-one (9): To a solution of **2g** (594 mg, 3.03 mmol) in anhydrous MeOH (5 mL) was added boron trifluoride·methanol complex (0.98 mL, 9.08 mmol). The solution was stirred for 5 h under reflux and subsequently cooled to −15 °C. After addition of *tert*-butyl nitrite (0.54 mL, 4.54 mmol) stirring was continued for 20 min, while raising the temperature to 0 °C. To this solution NaOAc (745 mg, 9.08 mmol) was added and a colourless solid was precipitated. The suspension was dissolved by addition of anhydrous MeOH (5 mL). To the mixture was added methyl acrylate (0.41 mL, 4.54 mmol) and $Pd(OAc)_2$ (34 mg, 5 mol%). The solution was stirred for 12 h at ambient temperature. After addition of activated charcoal (85 mg) the reaction mixture was stirred under an atmosphere of hydrogen (1 bar) for 24 h. The reaction was quenched by addition of hydrochloric acid (1 M, 20 mL) and extracted with MTBE (60 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica, MTBE) to afford **9** as a colourless solid; yield: 360 mg (2.21 mmol, 73%); mp 233 °C (reported in the literature:[23] 232 °C). ^{1}H NMR (300 MHz, methanol-d_4): $\delta = 6.95$ (d, $J = 8.1$ Hz, 1H), 6.41 (dd, $J = 8.1$, 2.4 Hz, 1H), 6.35 (d, $J = 2.4$ Hz, 1H), 2.83 (2H), 2.51 (2H); ^{13}C NMR (75 MHz, methanol-d_4): $\delta = 174.3$ (0), 158.1 (0), 139.8 (0), 129.7 (1), 116.1 (0), 111.0 (1), 104.0 (1), 32.2 (2), 25.6 (2); IR (KBr disc): $\tilde{\nu} = 3354$ (m), 1637 (s), 1357 (s), 1234 cm^{-1} (s); MS (ESI): $m/z = 164$ ($[M+H]^+$, 100), 122 (5), 99 (13); HR-MS (ESI): $m/z = 164.0721$, calcd. for $C_9H_{10}NO_2$ $[M+H]^+$: 164.0712; anal. calcd. for $C_9H_9NO_2$: C 66.2, H 5.6, N 8.6; found: C 66.0, H 5.6, N 8.4.

Acknowledgements

This work was performed in the course of a research and development project with the Zylum-Beteiligungsgesellschaft mbH & Co. Patente II KG, Schönefeld (Germany), in collaboration with the IP Bewertungs AG, Hamburg (Germany). Zylum-Beteiligungsgesellschaft mbH & Co. Patente II KG owns the underlying international patent applications.[30,38]

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