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Remarkable Electronic Effect on the Diastereoselectivity of the Heck Reaction of Methyl Cinnamate with Arenediazonium Salts: Formal Total Synthesis of (±)-Indatraline and (±)-Sertraline

Julio Cezar Pastre[a] and Carlos Roque Duarte Correia[a,*]

[a] Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, 13083-970 Campinas, São Paulo, Brazil
Fax: (+55)-19-3521-3023; e-mail: roque@iqm.unicamp.br

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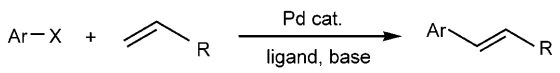
Abstract: An efficient and stereoselective protocol for the preparation of β,β-disubstituted acrylates in good to high yields by means of a Heck–Matsuda arylation was accomplished. The method employs a base- and ligand-free Heck arylation reaction of methyl cinnamate using both electron-deficient and electron-rich arenediazonium salts as electrophiles. The Heck reaction displays a remarkable electronic dependence regarding the diastereoselectivity of the arylation process, which correlates with the electronic nature of the arenediazonium salts employed. A rationale for the observed diastereoselectivity is presented. The overall methodology provides a convenient route to 3-arylindanones and 4-aryltetralones allowing the concise formal total syntheses of the therapeutically important psychoactive compounds (±)-indatraline and (±)-sertraline.

Keywords: arenediazonium salts; Heck reaction; indatraline; methyl cinnamate; palladium; sertraline

The palladium-catalyzed C–C coupling reactions constitute an important methodology in current organic synthesis.[1] Among the palladium-catalyzed C–C couplings, the Heck reaction[2] (Scheme 1) of aryl halides/triflates and alkenes holds a prominent position in view of its exceptional versatility, thus making it an exceptional tool for the synthesis of complex organic structures.[3]



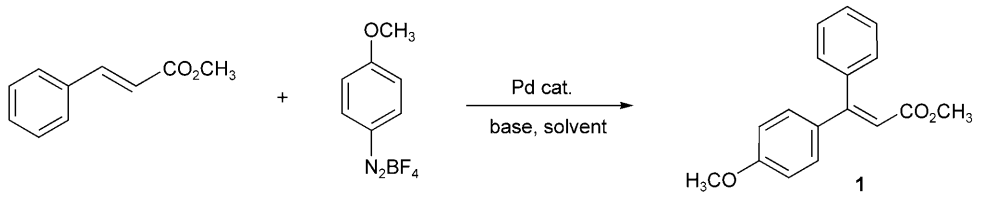
X = Cl, Br, I, OTf
R = alkyl, aryl, CO_2R, CN, etc.

Scheme 1. Heck reaction of aryl halides/triflates with alkenes.

Among the several arylating agents available to perform the Heck reaction, arenediazonium salts are probably the least explored ones (the Heck–Matsuda reaction), in spite of the fact that they offer considerable advantages (economical and environmental) over traditional electrophiles, such as aryl halides and aryl triflates.[4] First, Heck arylations employing arenediazonium salts do not require the use of phosphanes ("ligand-free conditions"), so reactions can be carried out under aerobic conditions making them much easier to handle than traditional protocols. Second, the arenediazonium salts are more reactive than the corresponding aryl halides in the palladium-catalyzed Heck reactions. Third, the Heck–Matsuda reactions can be carried out at lower temperature than the typical Heck reactions (usually over 100 °C), without added base or salt (such as silver chloride or thallium ethoxide), which extend the reaction scope to substrates with sensitive functional groups. Fourth, although certain aryl halides and triflates are difficult to synthesize, most arenediazonium salts can be easily generated from the corresponding aniline in high yields.[5] This is a significant consideration for combinatorial synthesis. Thus, application of arenediazonium salts in the metal-catalyzed coupling reactions could potentially simplify the synthesis of certain types of advanced intermediates, as well as reduce the number of steps involved in the synthesis of pharmaceuticals and agrochemicals.[6]

The Heck arylation of unsubstituted acrylates employing aryl halides/triflates or even arenediazonium salts is a well-established process.[3g] It has been used extensively as a benchmark protocol for the discovery of new palladium catalysts and/or to demonstrate new advances in the Heck arylation processes. However, reports on the use of more complex substituted acrylates are scarce in the literature. Usually these sub-

Table 1. Pd-catalyzed Heck arylation of methyl cinnamate with 4-methoxybenzenediazonium tetrafluoroborate.



Entry[a]	Pd Cat. (mol%)	Solvent	Base (3 equiv.)	*T*	*t* [h]	Conversion [%]	Yield [%][b]	*E*/*Z* ratio[c]
1	$Pd(OAc)_2$ (10)	MeCN	–	reflux	8	100	40	64:36
2	$Pd(OAc)_2$ (10)	MeOH	–	reflux	2	100	86	70:30
3	$Pd(OAc)_2$ (10)	EtOH	–	reflux	6	100	[d]	–
4	$Pd(OAc)_2$ (10)	*i*PrOH	–	reflux	6	29	83	68:32
5	$Pd(OAc)_2$ (10)	1,2-propanediol	–	100 °C	2	100	57	60:40
6	$Pd(OAc)_2$ (10)	MeOH	–	r.t.	5	100	67	80:20
7	$Pd_2(dba)_3$ (2.5)	MeOH	–	reflux	4	76	90	71:29
8[f]	$Pd_2(dba)_3$ (5)	MeCN	–	reflux	6	[e]	[d]	–
9	$Pd(OAc)_2$ (10)	MeOH	NaOAc	reflux	4	80	66	98:02
10	$Pd(OAc)_2$ (10)	MeOH	NaOAc	r.t.	14	88	63	97:03
11	$Pd(OAc)_2$ (10)	EtOH	NaOAc	reflux	6	55	40	98:02
12[g]	$Pd(OAc)_2$ (10)	MeOH	2,6-DTMP	reflux	2	100	35	78:22
13[h]	$Pd(OAc)_2$ (10)	MeOH	TBAA	reflux	4	75	56	98:02

[a] *Reaction conditions:* unless mentioned otherwise, 1.0 mmol of methyl cinnamate and 1.2 equiv. of 4-methoxybenzenediazonium tetrafluoroborate in 6 mL of solvent were used.
[b] Yields were calculated after flash chromatography and were based on the recovering of the starting material.
[c] Diastereoselectivities were determined by GC and GC/MS analysis, and confirmed by ^{1}H NMR.
[d] Complex mixture.
[e] Low conversion.
[f] 2.0 equiv. of the arenediazonium salt were used.
[g] 2,6-DTMP = 2,6-di-*tert*-butyl-4-methylpyridine; product of Michael addition of MeOH to **1** isolated in 53% yield.
[h] TBAA = *n*-tetrabutylammonium acetate.

strates are more resistant to Heck arylations, requiring relatively harsh reaction conditions to reach complete conversion and/or high yields of the desired adduct. From the synthetic standpoint this is a considerable limitation to the potential of the Heck reactions and poses a challenge to be addressed.

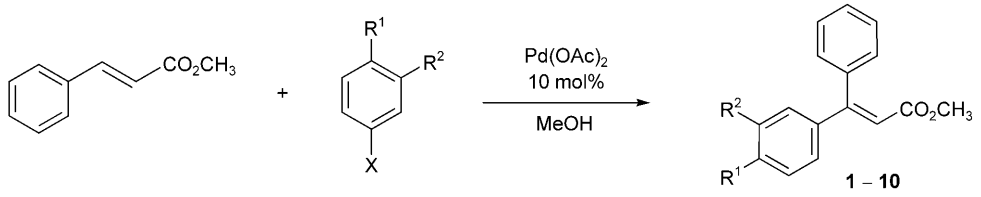
In particular for the arylation of cinnamic esters, several protocols have been developed during the last decades.[7] These protocols often require high temperatures,[7d,e,h,i] the use of DMF,[7c,d] DMA[7e] or TBAB[7h,i] as solvents, as well as the use of hindered tertiary amines as bases.[7e,g] As far as stereochemistry is concerned, high stereoselectivity has been obtained only in a few cases. Therefore, the development of a general, simple and highly stereoselective process that operates under mild reaction conditions constitutes an important synthetic objective.

In view of an increasing awareness of the synthetic advantages of the arenediazonium salts in the Heck reaction, we decided to investigate the feasibility of the Heck arylation of cinnamic esters.

For the Heck arylation of the commercially available methyl cinnamate, 4-methoxybenzenediazonium tetrafluoroborate was chosen as the initial arylating agent due to its exceptional thermostability and to allow introduction of an electron-rich aryl group, which is considerably less efficient when employing traditional Heck protocols. Some selected examples are presented in Table 1.

We first evaluated the effect of the solvent on the Heck reaction of methyl cinnamate using $Pd(OAc)_2$ as pre-catalyst, without addition of bases. Arylations were screened using common organic solvents usually employed in our laboratory for this type of reaction (like MeCN and alcohols). Arylation was observed in almost all solvents tested (Table 1). However, these were more efficient and faster in refluxing MeOH (entry 2). Heck arylations in ethanol, isopropyl alcohol and 1,2-propanediol resulted in more complex mixtures or low yields due to a rather fast transesterification (entries 3, 4 and 5). Arylations were completed in 2 h to provide the corresponding β,β-diarylpropionic ester **1** in good yields. Tendency for thermodynamic equilibration of the Heck adducts was observed when the reactions were followed by capillary GC – the ratio between adducts decreased with time. Based on this observation, we carried out the reaction at room temperature and the desired Heck adduct was isolated in a higher diastereoselectivity, favoring the (*E*) Heck adduct (entry 6). Also noteworthy is the

Table 2. Pd-catalyzed Heck arylation of methyl cinnamate with various arenediazonium salts.



Entry[a]	R^1	R^2	X	T [°C]	t [h]	Compound (yield [%][b])	E/Z ratio[c]
1	OCH_3	H	BF_4^-	reflux	2	**1** (86)	70:30
2	F	H	BF_4^-	reflux	2	**2** (67)	94:06
3	Cl	Cl	BF_4^-	reflux	1	**3** (70)	92:08
4	Cl	Cl	BF_4^-	r.t.	3	**3** (79)	97:03
5	NO_2	H	BF_4^-	reflux	2	**4** (98)	96:04
6	Cl	H	BF_4^-	reflux	1	**5** (95)	95:05
7	Br	H	BF_4^-	reflux	1	**6** (94)	81:19
8	OH	H	$CF_3CO_2^-$	reflux	2	**7** (93)	70:30
9	H	NO_2	BF_4^-	reflux	0.5	**8** (93)	97:03
10[d]	H	H	BF_4^-	r.t.	24	**9** (86)	–
11	OCH_3	OCH_3	BF_4^-	reflux	2	**10** (58)	60:40

[a] *Reaction conditions:* unless mentioned otherwise, 1.0 mmol of methyl cinnamate, 1.2 equiv. of arenediazonium tetrafluoroborate, and 10 mol% of $Pd(OAc)_2$ in 6 mL of MeOH were used.
[b] Yields were calculated after flash chromatography.
[c] Diastereoselectivities were determined by GC and GC/MS analysis and confirmed by ^{1}H NMR.
[d] 3.0 equiv. of the arenediazonium salt was added in small portions.

fact that $Pd_2(dba)_3$ as catalyst proved to be less efficient than $Pd(OAc)_2$, providing lower conversions or complex mixtures (entries 7 and 8).

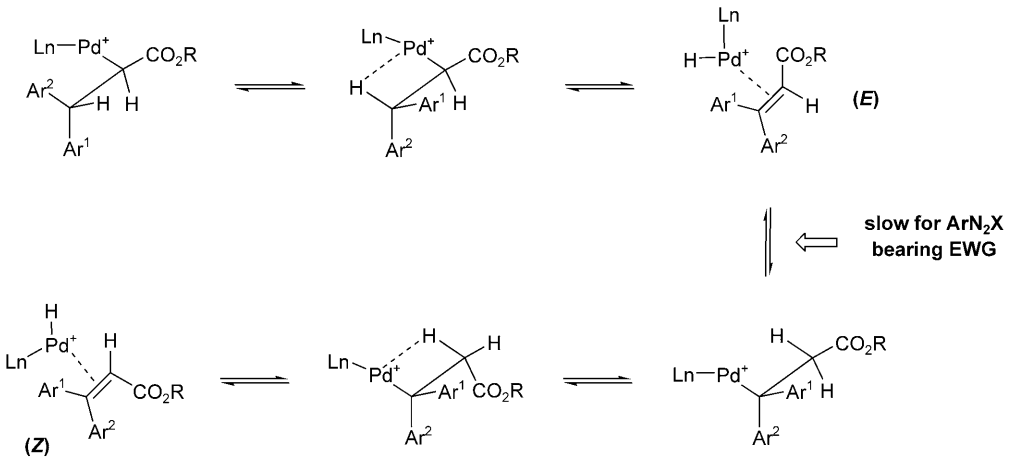
Regarding the stereochemical outcome, the stereoisomers are probably generated through the well-known elimination-reverse addition-elimination of the cationic PdH species. The low stereoselectivity observed in such systems has also been previously explained as a base-catalyzed isomerization (addition-elimination), leading to the preferred formation of the thermodynamic product. However, the use of bases in the Heck–Matsuda arylation of methyl cinnamate with 4-methoxybenzenediazonium tetrafluoroborate (entries 9–13) led to excellent diastereoselectivities (>97:03) in most cases, despite a significant drop in substrate conversion.[8]

The replacement of acetate bases by a soluble organic base such as 2,6-*di-tert*-butyl-4-methylpyridine led to a sharp decrease in the stereoselectivity with formation of the Heck adducts in a lower diastereomeric ratio (78:22, entry 12), along with 53% of the product of methanol Michael addition to the enoate. We hypothesize that the more soluble and hindered pyridine base is less effective in abstracting a proton from the cationic hydropalladium intermediate ligated to the olefin. On the other hand, acetate located at the coordinating shell of palladium could act as an effective base by intramolecular neutralization of $[PdH]^+$ through a five-membered transition state, as proposed by Calò and co-workers.[7i]

In order to evaluate the scope of this reaction, we further tested nine additional arenediazonium salts. The results, listed in Table 2, demonstrate that moderate to excellent yields of coupling products were obtained, with the diastereoselectivity depending on the nature of the arenediazonium salt used. Notably, diastereoselectivity was much higher with salts bearing electron-withdrawing groups than with electron-donating groups (compare entries 1 and 5). These results are very interesting since they demonstrate for the first time a remarkable dependence of the diastereoselectivity of the Heck arylation of cinnamates on the nature of the arenediazonium salts employed.[9] Furthermore, these results strongly suggest that the lower stereoselectivity observed for the Heck arylation of methyl cinnamate with electron-rich arenediazonium salts results from re-addition of $[PdH]^+$ to the double bond of the Heck enoates (Scheme 2).

By contrast, recently Nájera developed an oxime-derived palladacycle and applied it to preparation of trisubstituted olefins by a Heck arylation. However, when coupling ethyl cinnamate with either electron-poor and electron-rich aryl iodides, at 120 to 140 °C, the Heck adducts were obtained as a *ca.* 3:1 mixture of isomers.[7m] This example highlights the advantages of performing Heck arylations of cinnamates under milder reaction conditions.

It is also worth mentioning that *p*-nitro- and *m*-nitrobenzenediazonium tetrafluoroborate were equally suitable for the Heck arylation of methyl cinnamate



Scheme 2. Rationale for the stereoselectivity of the Heck arylation of methyl cinnamate.

(Table 2, entries 5 and 9). This observation is significant in view of the low yields of coupling products obtained by both Kikukawa[4b] and Sengupta[10] when employing these nitro-based diazonium salts in their ligand-free palladium-catalyzed coupling reactions.

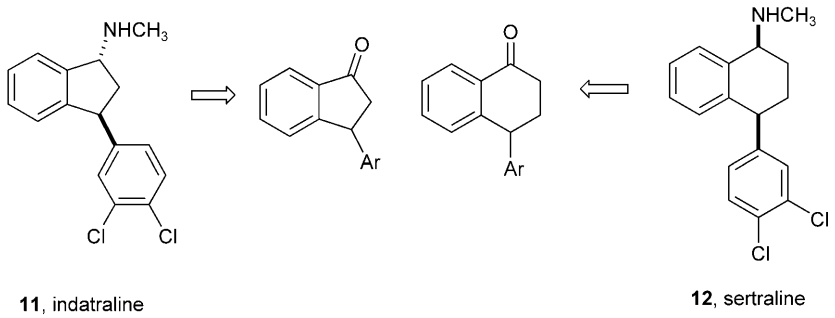
In entry 8, *p*-hydroxybenzenediazonium trifluoroacetate was used instead of the usual tetrafluoroborate salt due to difficulties in the preparation of the latter salt. With the trifluoroacetate salt the Heck adduct was obtained in excellent yields, and the diastereoselectivity paralleled that observed for the *p*-methoxy-substituted salt.

Benzenediazonium tetrafluoroborate was a challenge for the Heck arylation of methyl cinnamate, probably due to its low thermostability. To overcome this difficulty, the reaction was conducted at room temperature and the salt was added in small portions to ensure complete conversion. To our delight, the desired Heck adduct was obtained in a good 86% yield (entry 10).

The development of an efficient process for the Heck arylation of β-aryl acrylates is of significant utility since β,β-diarylpropionic esters are key intermediates in the synthesis of many important drugs, like the angiotensin II antagonists,[11] the platelet-activating factor antagonists,[12] and the SRS-A antagonists (slow-reacting substance of anaphylaxis).[13]

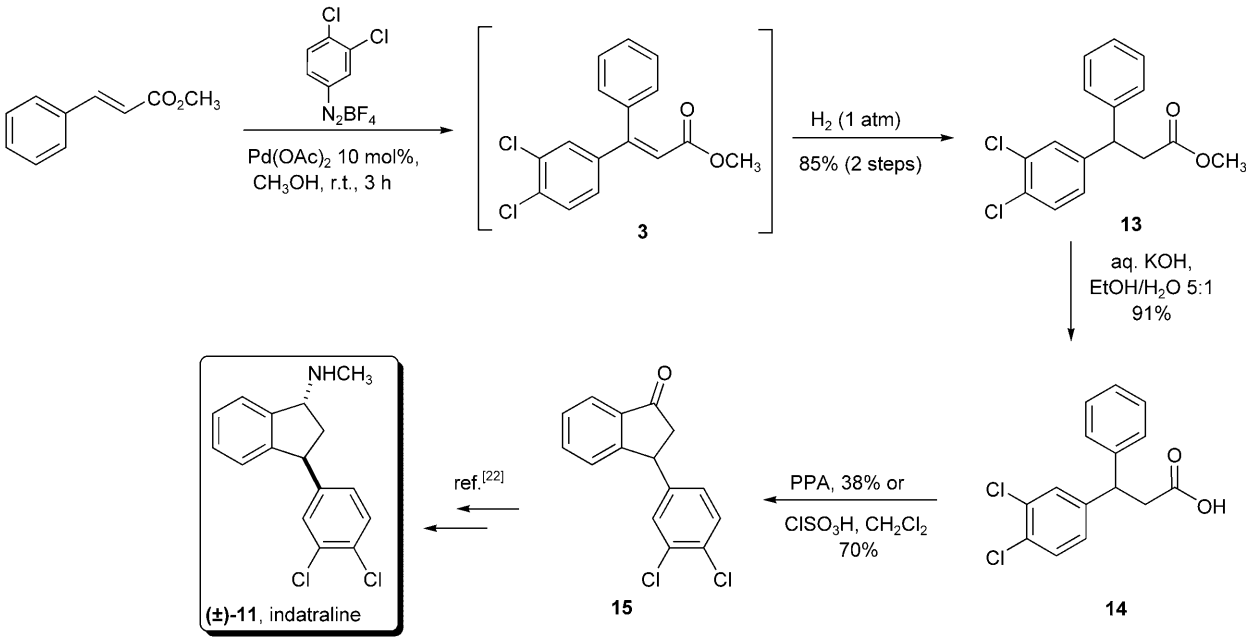
To highlight the versatility of the procedure developed herein, our planning also included the application of these Heck arylations in the synthesis of pharmacologically active compounds. One of the objectives of this initial investigation was the construction of the indane ring[14] and the tetrahydronaphthalene core[15] that are present in the structure of bioactive and pharmaceutically interesting molecules, such as indatraline and sertraline, respectively.

Indatraline **11** (Lu 19-005, Figure 1) is a potent psychoactive compound with high binding and inhibitory activity for neuronal monoamine reuptake sites, including dopamine and serotonin transporters.[16] *In vivo* dialysis and behavioral studies have indicated a potent dopaminergic mechanism of action for indatraline[17] with a long period of action.[18] In addition, studies in monkeys indicated that indatraline reduced cocaine self administration.[19] Sertraline **12** (marketed as Zoloft®) acts on the central nervous system as a selective serotonin reuptake inhibitor (SSRI)[20] and is an important commercial drug for the treatment of



11, indatraline **12**, sertraline

Figure 1. Chemical structures of indatraline and sertraline.



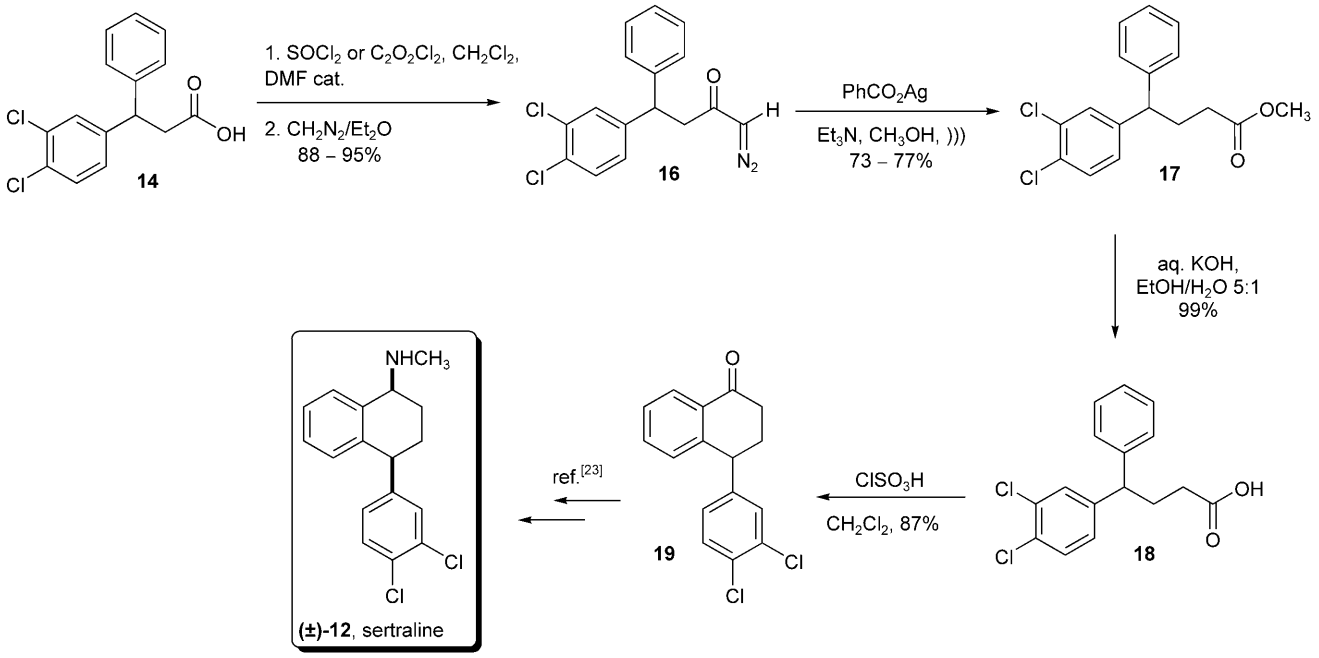
Scheme 3. Formal total synthesis of (±)-indatraline.

depression, dependency, and other anxiety-related disorders.[21] In spite of several available methodologies for preparing indatraline and sertraline, there is the need for new strategies to prepare the 3-arylindane and 4-aryltetrahydronaphthalene systems displayed by this class of compounds.

We first turned our attention to the synthesis of the precursor of indatraline. Thus, methyl cinnamate was subjected to the Heck arylation with 3,4-dichlorobenzenediazonium tetrafluoroborate at room temperature followed by an *in situ* catalytic hydrogenation of the Heck adduct **3** (Scheme 3), to provide the saturated β,β-diarylated product **13** in 85% yield (over 2 steps). Control of the hydrogenation step is crucial since we identified the formation of dehalogenated by-products under GC/MS analysis after one hour. Next, hydrolysis of the ester function with aqueous KOH gave the corresponding acid **14** in 91% yield. Subsequent cyclization using polyphosphoric acid (PPA) or chlorosulfonic acid afforded the known precursor of (±)-indatraline **15** in 38% and 70% yields, respectively, whose spectroscopic data were identical to those described in the literature (Scheme 3).[22]

Aiming at intercepting a known advanced intermediate for the synthesis of sertraline, the diarylated acid **14** was subjected to the corresponding homologation process using the Arndt–Eistert protocol (Scheme 4). Preparation of diazo ketones *via* mixed carbonic anhydride proved ineffective in our substrate. However, treatment of the corresponding acyl chloride with diazomethane gave the desired α-diazo ketone **16** in high yields (88–95%), which was then subjected to the Wolff rearrangement using silver benzoate under ultrasound irradiation. Next, hydrolysis of the methyl ester **17** with aqueous KOH gave the corresponding acid homologue **18** in 99% yield. Finally, cyclization with chlorosulfonic acid afforded the tetralone **19** in 87% yield, which can be converted to (±)-sertraline using conditions described in the literature.[23]

In conclusion, we have developed an efficient and stereoselective method for the preparation of β,β-diarylacrylates in good to high yields by means of a Heck reaction with arenediazonium tetrafluoroborates. This method is applicable to the coupling of both electron-deficient and electron-rich arenediazonium salts and displays a remarkable diastereoselectivity dependence on the electronic nature of the arenediazonium salts. These results corroborate the hypothesis of isomerization of the Heck adduct by a PdH re-addition to the double bond. Moreover, we describe concise and convenient routes for the preparation of 3-arylindanones and 4-aryltetralones employing a base- and ligand-free, palladium-catalyzed Heck arylation of methyl cinnamate as the key step. Application of this protocol allowed the concise formal total syntheses of (±)-indatraline and (±)-sertraline. Furthermore, thanks to the high degree of stereoselectivity of the Heck arylation when using the dichloro-based arenediazonium salt, we are now in a position to explore the asymmetric synthesis of both indatraline and sertraline, *via* an enantioselective reduction of the Heck adduct. These results will be reported in due course.



Scheme 4. Formal total synthesis of (±)-sertraline.

Experimental Section

Typical Experimental Procedure

To a solution of methyl cinnamate (161 mg; 1.0 mmol) in 6.0 mL of methanol was added, at once, a mixture of the arenediazonium salt (1.2 mmol; 1.2 equiv.) and palladium(II) acetate (24 mg; 10 mol%). The reaction mixture was immersed in an oil bath and heated at reflux until TLC and GC analyses indicated complete consumption of the methyl cinnamate. After cooling, the mixture was filtered through a pad of Celite and purified by flash column chromatography (ethyl acetate/hexane) to give the corresponding Heck adduct in the yields and diastereoselectivities shown in Table 1 and Table 2.

Acknowledgements

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