Heck Arylation of Maleic Anhydrides Using Arenediazonium Tetrafluoroborates: Synthesis of Mono- and Diarylated Maleic Anhydrides and of the Marine Alkaloids Prepolycitrin A and Polycitrin A

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Dedicated to Professor Richard F. Heck for his outstanding contributions to the field of organometallic chemistry

Abstract: The Heck arylation of maleic anhydrides using arenediazonium tetrafluoroborates was investigated. Symmetrical and unsymmetrical 3,4-diarylmaleic anhydrides, some of them showing interesting fluorescent properties, were prepared in one or two steps from cheap and commercially available maleic anhydride. This Heck arylation methodology constitutes a new and direct entry to the synthesis of arylated maleic anhydride materials, natural products and their derivatives, as demonstrated with the total syntheses of the marine alkaloids prepolycitrin A and polycitrin A and with the synthesis of a N-protected fluorescent phenylalanine.

Key words: arenediazonium tetrafluoroborates, Heck arylation, 3,4-diarylmaleic anhydrides, polycitrin A, fluorescent materials

Arylated maleic anhydrides and maleimides constitute an important and highly diversified class of compounds. The aryl maleic anhydride and maleimide moieties are present in the skeleton of marine natural products, such as prepolycitrin A,[1] and polycitrins A and B,[2] and in many useful fluorescent compounds as illustrated in Figure 1.[3] A close relationship between these two skeletons is evident by the readily interchange between maleic anhydrides and maleimides.[4]

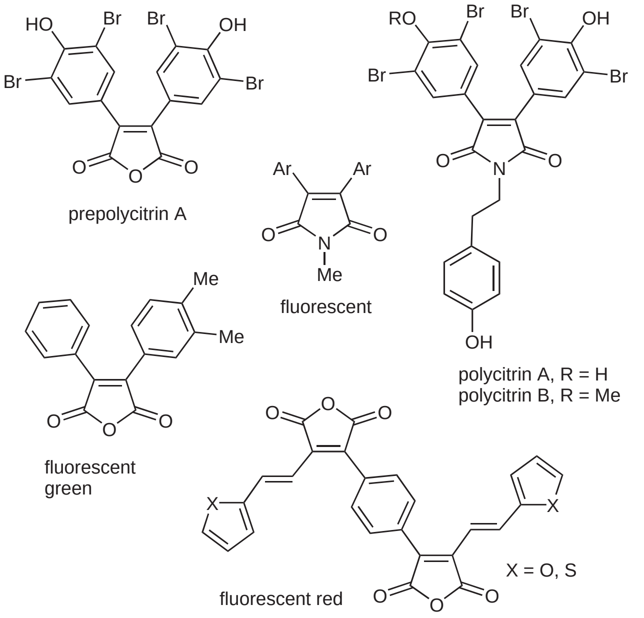

Figure 1 Examples of arylated maleic anhydrides and derivatives

The synthesis of mono- and diarylated maleic anhydrides is well-documented in the literature,[3b,5] and to the best of our knowledge one of the most effective and general methods for their synthesis was developed by Koelsh and Wawzonek.[6] This method relies on the Perkin condensation of aryl acetic acids with glyoxylic acids. However, despite its versatility and generality this method often depends on acetic and glyoxylic acids, which may not be readily available.

A more direct and modern approach to this class of compounds is the Heck arylation of maleic anhydrides or maleimides. Somewhat surprising, this approach is rarely reported in the literature, and the few reports available are restricted to the synthesis of the monoarylated maleimides and maleic anhydrides.[7] For the synthesis of diarylated maleimides a Suzuki–Miyaura cross-coupling was reported recently from a diiodo maleimide intermediate, which required several steps for its synthesis.[8] The Meerwein reaction using arenediazonium chlorides has also been successfully used in the synthesis of arylated maleic anhydrides and maleimides.[9] However, the Meerwein arylations have been usually plagued with low yields, the need for a strict control of the pH (3–5), the use of considerable amounts of the copper salts, and reproducibility problems.[9a]

During the course of a recent investigation on the Heck arylation of α,β-unsaturated carbonyl compounds with arenediazonium tetrafluoroborates we were intrigued by a very facile arylation of maleic anhydride to provide a 43:57 mixture of the monoarylated and the highly fluorescent diarylated maleic anhydride [Scheme 1, (1)].[10] This result was even more surprising when it was compared with the Heck arylation of dimethyl maleate, which provided the monoarylated dimethyl maleates (*E*/*Z* mixture, 2:1 ratio) as major reaction adducts [Scheme 1, (2)].[10b]

Although yields for the Heck arylation of maleic anhydride were somewhat low at that time, we felt that a direct approach to this class of compounds could be developed from these results.

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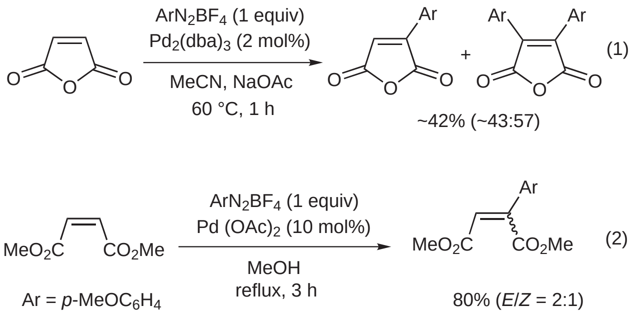
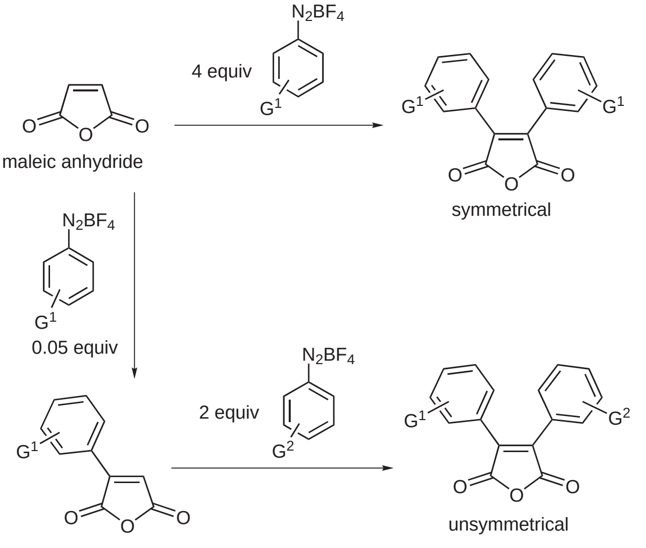


Scheme 1 Comparing results of the Heck arylations of maleic anhydride and dimethyl maleate with arenediazonium tetrafluoroborates

Therefore, in view of the interesting properties of the arylated maleic anhydrides and their derivatives we started an investigation with the aim of preparing these compounds in a concise manner, employing inexpensive and commercially available materials. In this paper, we present our preliminary results regarding the synthesis of arylated maleic anhydrides, and the application of this protocol in the shorter synthesis of the marine natural products prepolycitrin A and polycitrin A. As depicted in Scheme 2, mono- and diaryl maleic anhydrides can be readily and selectively prepared by the Heck arylation of maleic anhydride with arenediazonium tetrafluoroborates.

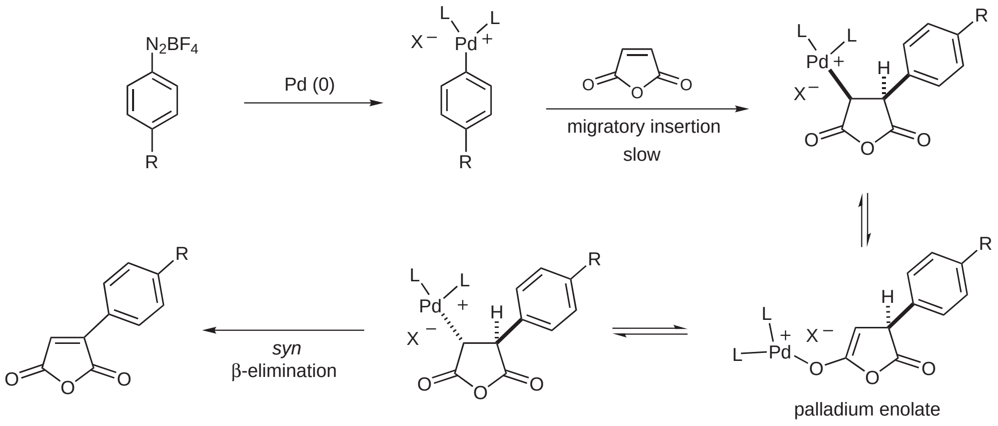


Scheme 2 Synthesis of symmetrical and unsymmetrical maleic anhydrides by Heck arylations using arenediazonium tetrafluoroborates

We started out evaluating the scope of the Heck arylation of maleic anhydride employing several arenediazonium tetrafluoroborates (Table 1). At the same time we tried to optimize yields by varying reaction parameters such as: solvent, temperature, base, palladium catalysts and the use of additives. After much experimentation we found that the use of Pd(OAc)$_2$ or Pd$_2$(dba)$_3$ as catalyst, NaOAc or Li$_2$CO$_3$ as base and acetonitrile as solvent at temperatures between 65 °C and reflux (entries 10–16) constitutes the best reaction conditions for the synthesis of the arylated maleic anhydrides.[11] These mono- and diarylated maleic anhydrides can be selectively prepared by varying the amount of arenediazonium salt according to that described in Scheme 2.[12] The use of a base (NaOAc or Li$_2$CO$_3$) and higher temperatures (65–100 °C) seem critical for the arylation of maleic anhydride, since its absence or the use of other bases[11] furnished only trace amounts of the desired products, together with many side products (entry 4). Best performances were observed in acetonitrile as solvent, with no reaction observed in MeOH or an ionic liquid (entries 6 and 7). Curiously, Heck arylation of dimethyl maleate worked best in methanol as solvent, and without the need of any external base [Scheme 1, (2)].

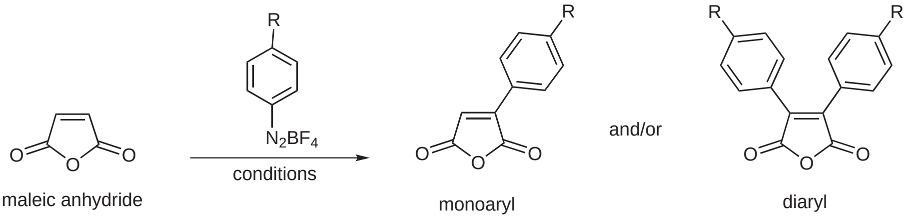
As shown in Table 1, arenediazonium tetrafluoroborates bearing strong electron-donating (ED) groups (R = OMe, NHCO$_2$Me) furnished good yields (60–75%) of the mono- and diarylated maleic anhydrides, whereas *p*-tolyldiazonium salt furnished only 31% of the diarylated Heck adduct (entry 13). Arenediazonium salts bearing electron-withdrawing (EW) groups (entries 17 and 18) resulted in complex mixtures. To our surprise, these latter results with EW groups are in sharp contrast with those we obtained for the Heck arylation of acrylate derivatives. With cyclic and acyclic acrylates, efficient arylations were observed not only with electron-donating arenediazonium salts but also with those bearing strong electron-withdrawing substituents, such as halogens and nitro groups.[10a] The reasons for such behavior are not clear at present. A possible explanation might be the stability of the key EW-substituted cationic arylpalladium intermediate (Scheme 3) in the reaction medium (MeCN vs. MeOH) and/or the distinct mechanisms operating in both cases. With acyclic acrylates a free-rotating adduct is formed after migratory insertion, which undergoes a facile β-elimination to generate the Heck adduct. Most probably, in the case of maleic anhydrides there is the need for palladium isomerization via a cyclic cationic palladium enolate whose reactivity and stability are uncertain.

The results presented in Table 1 clearly indicated the feasibility of the Heck arylation to prepare monoarylated and symmetric diarylated maleic anhydrides. However, aiming at adding flexibility to the Heck arylation methodology, and to extend its applicability, we investigated the conversion of monoarylated maleic anhydrides into the unsymmetrical diarylated compounds. As illustrated in Table 2, monoarylated maleic anhydrides can be cleanly converted into the unsymmetrical 3,4-diaryl maleic anhydrides, although only in moderate yields.[12]



Scheme 3 Rationale for the monoarylation of maleic anhydrides with arenediazonium tetrafluoroborates

Table 1 Heck Arylation of Maleic Anhydride with Arenediazonium Tetrafluoroborates



Entry	R (equiv)	Reaction conditions[a]	Yield (%)[b]	mono:di[c]
1	MeO (2)	$Pd_2(dba)_3$, NaOAc, MeCN, r.t., 1 h	0	–
2	MeO (1)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	ca. 42[d]	43:57
3	MeO (2)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	ca. 50[d]	15:85
4	MeO (2)	$Pd_2(dba)_3$, MeCN, 65 °C, 1 h	Complex mixture	–
5	MeO (4)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	48	02:98
6	MeO (4)	$Pd(OAc)_2$, NaOAc, MeOH, 65 °C, 1 h	No reaction	–
7	MeO (4)	$Pd(OAc)_2$, 1-butyl-3-methylimidazolium hexafluorophosphate, 65 °C, 5 h	No reaction	–
8	MeO (4)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (8%), dihydrofuran (4%), r.t., 1 h	20[d]	40:60
9	MeO (4)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), 65 °C, 1 h	45	02:98
10	MeO (4)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), reflux, 1 h	60	>01:99
11	MeO (0.05)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	65	96:04
12	MeO (0.05)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), reflux, 1 h	72	98:02
13	Me (4)	$Pd_2(dba)_3$, NaOAc, MeCN, r.t., ultrasound, 2 h	31	10:90
14	Me (0.05)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), reflux, 1 h	60	98:02
15	$NHCO_2Me$ (4)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), reflux, 1 h	68	>01:99
16	$NHCO_2Me$ (0.05)	$Pd(OAc)_2$, NaOAc, MeCN, anisole (4%), dihydrofuran (2%), reflux, 1 h	75	>99:01
17	NO_2 (4)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	Complex mixture	–
18	Cl (4)	$Pd_2(dba)_3$, NaOAc, MeCN, 65 °C, 1 h	Complex mixture	–

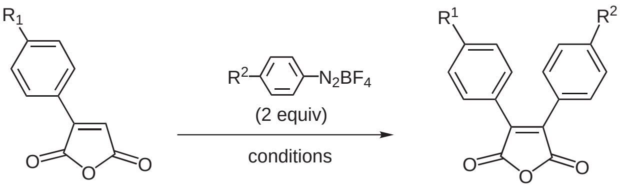
[a] $Pd_2(dba)_3$ (2 mol%); $Pd(OAc)_2$ (4 mol%).

[b] Yields are for isolated products, except when indicated otherwise. Yields for the diarylated products are based on maleic anhydride, and those for the monoarylated adducts on the arenediazonium tetrafluoroborate.

[c] Ratio of mono- and diaryl maleic anhydrides determined by capillary GC prior to isolation and purification of the Heck adducts.

[d] Yields referring to a mixture of the mono and diarylated Heck adducts (single spot on TLC).

Table 2 Synthesis of Unsymmetrical Diaryl Maleic Anhydrides



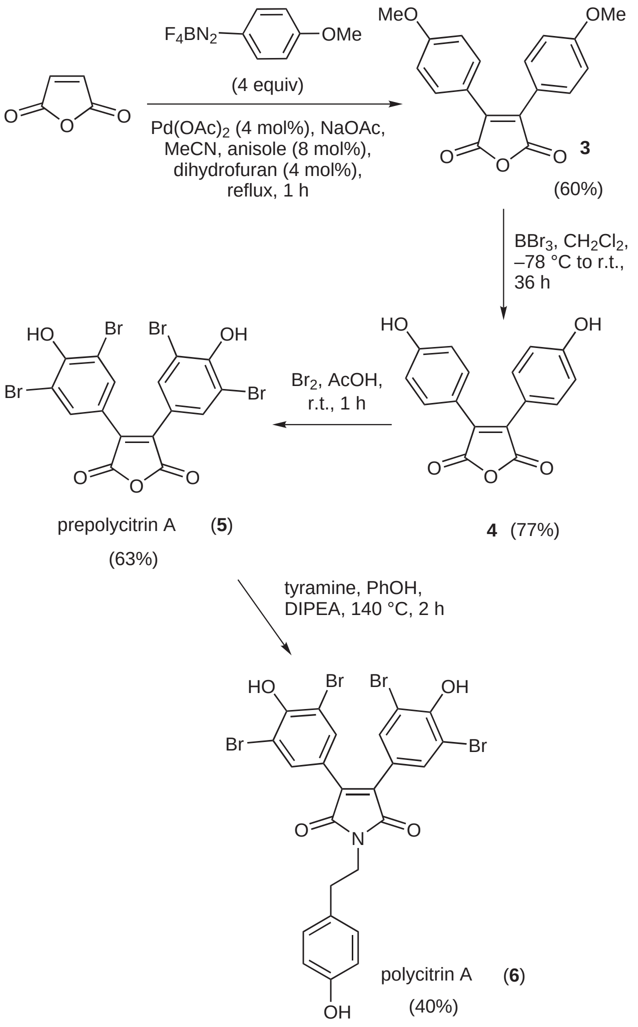
Entry	R^1	R^2	Yield (%)
1[a]	MeO	Me	50
2[b]	$NHCO_2Me$	MeO	65
3[b]	MeO	Me	48
4[b]	$NHCO_2Me$	Me	45

[a] $Pd_2(dba)_3$ (2 mol%), NaOAc, MeCN, 65 °C, 1 h.

[b] $Pd(OAc)_2$ (4 mol%), dihydrofuran (4 mol%), anisole (8 mol%), NaOAc, MeCN, reflux, 1 h.

The possibility of preparing symmetrical and unsymmetrical arylated maleic anhydrides from maleic anhydride made the methodology attractive for the synthesis of the marine alkaloids prepolycitrin A and polycitrin A (Figure 1). These compounds were isolated from the marine ascidian *Polycitor* sp. by Kashman and co-workers in 1994.[2] Regarding the synthesis of polycitrins, there are only two examples in the literature. In 1995 Steglich[13] reported the biomimetic synthesis of polycitrin A, while in 2000 Beccalli reported the total synthesis of polycitrin B.[14] Steglich synthesized polycitrin A in a rather straightforward fashion starting from 3,4-di(4-methoxyphenyl)maleic anhydride. However, Steglich's route to this arylated maleic anhydride consumed four steps from 4-methoxyphenylacetic acid. Based in part on the work reported by Steglich and Beccalli, we synthesized the marine alkaloids prepolycitrin A and polycitrin A in a more concise manner employing the direct Heck arylation of maleic anhydride developed above (Table 1).

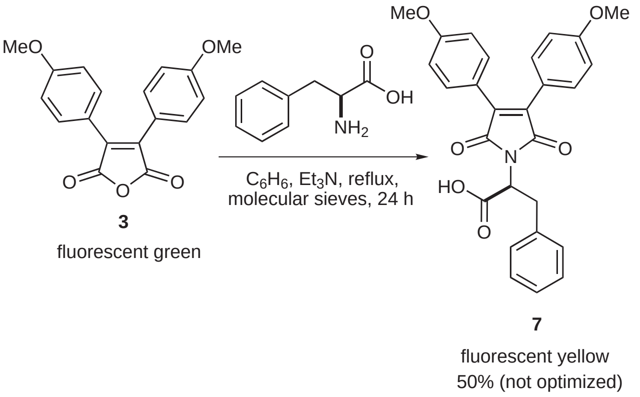
The key 3,4-di(4-methoxyphenyl)maleic anhydride (**3**) could be readily prepared in just one step from maleic anhydride in 60% isolated yield (see Table 1, entry 10). Demethylation of the diarylated anhydride **3** in the presence of BBr_3 in CH_2Cl_2 cleanly afforded the corresponding phenol **4** in 77% yield. Bromination of phenol **4** with Br_2 in acetic acid, followed by quenching with aqueous Na_2SO_3 solution, furnished the unstable brominated phenol corresponding to prepolycitrin A (**5**) in 63% yield. The Steglich group reports a 83% yield for a similar transformation.[13] However, in our hands, isolated yields stayed at ca. 60% for all the reactions performed. Finally, polycitrin A **6** was obtained in ca. 40% yield by heating a mixture of recrystallized **5** with tyramine, Hünig's base and phenol at 140 °C for 2 hours. Due to the instability of prepolycitrin A (**5**), an alternative procedure was undertaken. The crude dibromophenol **5**, obtained from the bromination of phenol **4**, was heated with tyramine to afford polycytrin A (**6**) in 30% yield for the two steps (Scheme 4).



Scheme 4 Total synthesis of prepolycitrin A and polycitrin A

Many diarylated maleimides and maleic anhydrides display interesting fluorescent and biological properties.[3a,15] These frameworks constitute readily available compounds with potential for application as new fluorophores and as probes to track biomolecules.[16] As an example, the yellow fluorescent phenylalanine **7** was readily prepared from the green fluorescent diarylated maleic anhydride **3** by simply heating it in benzene with phenylalanine as illustrated in Scheme 5. The diaryl maleic anhydride serves not only as a fluorescent probe, but also as an amino protecting group.

In summary, we have demonstrated that the direct Heck arylation of maleic anhydride with arenediazonium tetrafluoroborates is a viable alternative for the synthesis of mono- and diaryl maleic anhydrides.[17] Yields are generally moderate to good when employing arenediazonium salts bearing strong electron-rich substituents, whereas complex mixtures resulted when using arenediazonium salts bearing electron-withdrawing substituents. The methodology is amenable to the preparation of symmetrical and unsymmetrical maleic anhydrides/maleimides. The potential of these Heck arylations was demonstrated



Scheme 5 Synthesis of a N-protected and fluorescent phenylalanine

with the syntheses of prepolycitrin A (**5**), polycitrin A (**6**), and of the fluorescent N-protected phenylalanine **7**. Further studies aiming at extending these Heck arylations to a more diverse class of arylated maleic anhydrides as well as new applications for the fluorescent materials prepared herein are in progress and will be reported in due course.

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(11) Reactions using $Pd_2(dba)_3$ as catalyst generate a number of colored side products, probably due to the Heck arylation of the ligand dba. A better Pd(0) source was obtained by in situ reduction of $Pd(OAc)_2$ using dihydrofuran, and anisole as additive. This procedure provided a finely dispersed Pd(0) in MeCN (see ref. 17). Arylation failed with other bases, such as: 2,6-di(*tert*-butyl)-4-methylpyridine, Et_3N, imidazole, K_2CO_3 and $BaCO_3$.

(12) Superstoichiometric amount of the arenediazonium salts (2 or 4 equiv) is not strictly required for the synthesis of the diarylated adducts. However, the use of excess of this reagent leads to shorter reaction times and higher yields.

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(17) **Typical Experimental Procedure.**
To a solution of 4.5 mg of $Pd(OAc)_2$ in 3 mL of MeCN was added anisole (0.8 mL of a 0.1 M solution in MeCN) and 2,3-dihydrofuran (0.2 mL of a 0.1 M solution in MeCN). After 5 min, 49 mg of maleic anhydride (0.5 mmol), 123 mg of NaOAc (1.5 mmol) and 443 mg of 4-methoxybenzene-diazonium tetrafluoroborate (2 mmol) were added and the reaction mixture refluxed for 1 h. After cooling, the reaction mixture was diluted with 15 mL of EtOAc and filtered through a short pad of Celite®. The solvent was then evaporated in vacuo and the residue flash chromatographed (SiO_2, hexane–EtOAc = 8:2) to provide 93 mg (60% yield) of the Heck adduct **3** as homogeneous material by TLC.