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Unprecedented Substoichiometric Use of Hazardous Aryl Diazonium Salts in the Heck-Matsuda Reaction via a Double Catalytic Cycle

François Le Callonnec, Eric Fouquet, and François-Xavier Felpin*

Université de Bordeaux, UMR CNRS 5255, Institut des Sciences Moléculaires,
351 Cours de la Libération, Talence, 33405 France

fx.felpin@ism.u-bordeaux1.fr

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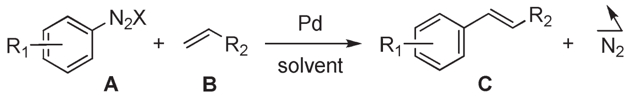
ABSTRACT

The first Heck-Matsuda reaction using a catalytic amount of diazonium salts has been discovered. The reaction proceeds through an unprecedented double catalytic cycle in which the electrophile is in situ generated through the reaction advancement. This concept features mild and safe conditions as hazardous aryl diazonium salts are not isolated anymore. Importantly, this sustainable procedure generates only environmentally friendly byproduct such as *t*-BuOH, H_2O, and N_2.

The Heck-Mizoroki reaction has become a standard in the toolbox of every synthetic chemist. The simultaneous observation, in the laboratories of Mizoroki[1] and Heck,[2] that aryl halides could be coupled with olefins in the presence of a palladium catalyst, has opened the way for 40 years of impressive achievements directed at the development of numerous efficient catalytic systems.[3] In October 2010, the Nobel Prize in chemistry was awarded to Richard F. Heck in recognition of his discovery.[4]

A far less explored variant of this coupling, known as the Heck–Matsuda reaction, entails the use of aryl diazonium salts as highly reactive aryl halide surrogates (Scheme 1).[5] The superelectrophile properties of aryl diazonium salts allows the reaction to proceed under mild conditions ($T <$ 60 °C), without the need of ligand, and even sometimes, base. The simple and efficient experimental procedure features many advantages, including energy, cost, and waste benefits that are of interest for the development of sustainable processes.

Scheme 1. General Representation of the Heck–Matsuda Reaction



Aryl diazonium salts have been discovered in the middle of the 19th century by Johann Peter Griess who was working on azo-compounds as dyes and pigments.[6] They are a class of superelectrophile with the common structure of R-N_2X where R is an aryl or heteroaryl fragment and X is a weakly nucleophilic organic or inorganic anion. A number of diazonium salts are commercially available;

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(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581–582.

(2) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322.

(3) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 2.

(4) The Nobel Prize in Chemistry 2010 was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.

(5) (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622–4643. (b) Taylor, J. G.; Venturini Moro, A.; Correia, R. C. D. *Eur. J. Org. Chem.* **2011**, 1403–1428. (c) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815–3831.

(6) Griess, P. *Liebigs Ann. Chem.* **1858**, *106*, 123–125.

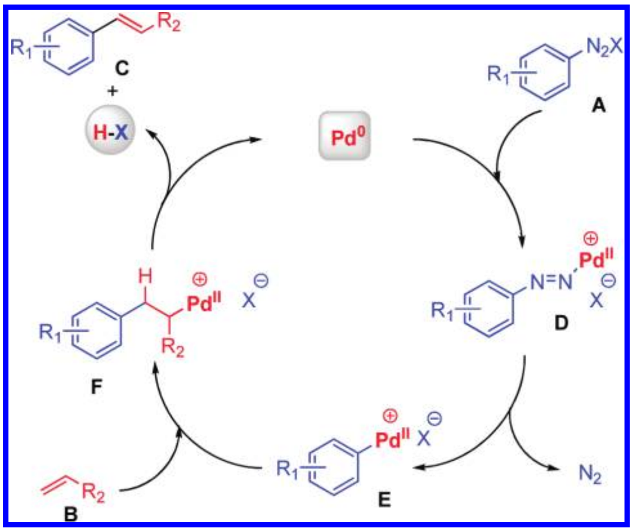
10.1021/ol200752x

however, the high nucleofugic properties of the diazonium function makes these compounds potentially hazardous, especially on large scale. By the way, whenever aryl diazonium salts have been involved in several industrial processes, including a Heck−Matsuda transformation for the preparation of herbicide Prosulfuron at Syngenta,[7] safety issues hampered further developments. Indeed, the stability of aryl diazonium salts is mostly dependent on the associated counterion, although the aryl structure should also be considered. For instance, while aryl diazonium chlorides[8] and acetates are unstable above 0 °C, their tetrafluoroborate,[9] tosylate,[10] and disulfonimide[11] counterparts are usually more stable crystalline salts. However, as the stability cannot be anticipated due to the absence of well-defined rules, safety issues need to be addressed for chemists who do not want to play Russian roulette.

Heck−Matsuda reactions have been mostly carried out with diazonium salts having a tetrafluoroborate anion.[12] Crystalline salts are typically prepared from the corresponding aniline by action of a nitrite in the presence of fluoroboric acid or $BF_3\cdot Et_2O$.[13] A safer protocol, involving the in situ preparation of diazonium salts, has been elegantly proposed by Andrus and co-workers.[14] However, the procedure still required the use of an equimolar quantity of $BF_3\cdot Et_2O$ and furnished styrene type compounds with quite modest yields (17−62%).

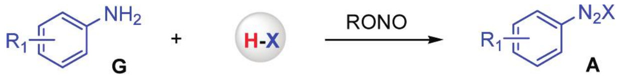
With the aim of developing a safe and environmentally benign strategy, we sought for a conceptually novel approach. Our idea grew up after a detailed survey of the mechanism involved in the Heck−Matsuda reaction (Scheme 2). Indeed, it has been well established that palladium intermediates bear a positive charge during the catalytic cycle.[15] This uncommon feature renders very active the intermediates **D** to **F** and optional the use of a base. As a consequence, in the absence of a base, one molar equivalent of a nontrapped acid (HX) is generated per equivalent of olefin **C** formed.

Scheme 2. Catalytic Cycle of the Heck−Matsuda Reaction



We also realized that a stoichiometric use of the same acid was also required for the prior formation of the diazonium salt from the corresponding aniline **G** (Scheme 3).

Scheme 3. General Preparation of Diazonium Salts



With these observations in mind, we anticipated that a catalytic amount of HX could be used in a cascade diazonium formation-Heck coupling process, according to the following unprecedented double catalytic cycle (Scheme 4). In the presence of *t*-BuONO aniline **G** would be transformed into its corresponding hydroxydiazene **H** with the concomitant formation of *t*-BuOH. Treated by a catalytic amount of an acid HX, the hydroxydiazene **H** would give the diazonium salt **A**. A standard palladium-catalytic cycle, involving an oxidative addition, an olefin insertion, and a reductive elimination, would furnish the targeted coupling product **F** as well as both Pd(0) and acid catalysts necessary for each catalytic cycle. As the only byproduct formed would be *t*-BuOH, H_2O, and N_2, such an approach should be of great interest toward the quest of sustainable processes.

Pursuing our challenging hypothesis, we initially focused on 4-nitroaniline **1a** as model substrate since nitro-substituted aryl diazonium salts frequently failed to participate in Heck−Matsuda reactions[16] due to a high tendency

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(7) (a) Baumeister, P.; Meyer, W.; Oertle, K.; Seifert, G.; Steiner, H. *Chimia* **1997**, *51*, 144–146. (b) Baumeister, P.; Seifert, G.; Steiner, H. EP0584043, 1992.

(8) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31–36.

(9) Flood, D. T. *Org. Synth.* **1943**, *2*, 295–298.

(10) Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K.-W. *Org. Lett.* **2008**, *10*, 3961–3964.

(11) (a) Barbero, M.; Crisma, M.; Degani, I.; Fochi, R.; Perracino, P. *Synthesis* **1998**, 1171–1175. (b) Artuso, E.; Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Tetrahedron* **2006**, *62*, 3146–3157.

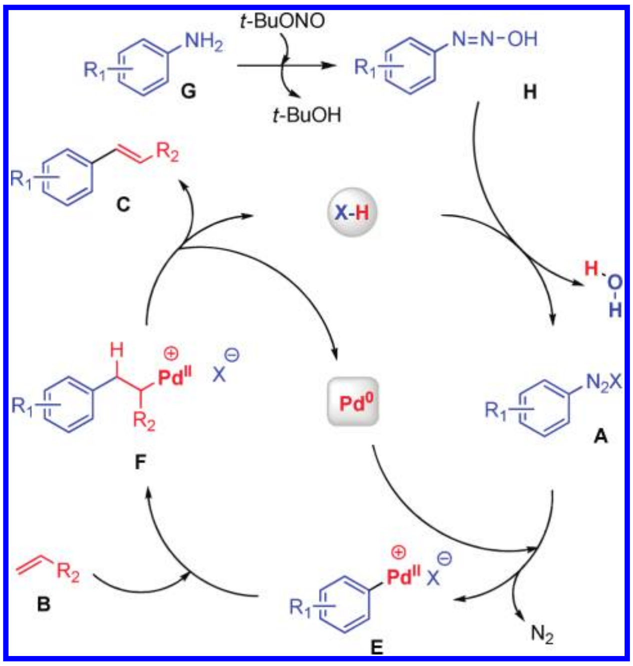
(12) For some relevant examples, see: (a) Darses, S.; Pucheault, M.; Genêt, J.-P. *Eur. J. Org. Chem.* **2001**, 1121–1128. (b) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem.—Eur. J.* **2002**, *8*, 3901–3906. (c) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305–308. (d) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221–224. (e) Garcia, A. L. L.; Carpes, M. J. S.; De Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050–1053. (f) Pastre, J. C.; Correia, C. R. D. *Org. Lett.* **2006**, *8*, 1657–1660. (g) Peixoto da Silva, K.; Godoi, M. N.; Correia, C. R. D. *Org. Lett.* **2007**, *9*, 2815–2818. (h) Cesar-Pastre, J.; Roque Duarte Correia, C. *Adv. Synth. Catal.* **2009**, *351*, 1217–1223. (i) Schmidt, B.; Hölter, F. *Chem.—Eur. J.* **2009**, *15*, 11948–11953. (j) Schmidt, B.; Hölter, F.; Berger, R.; Jessel, S. *Adv. Synth. Catal.* **2010**, *352*, 2463–2473. (k) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983–1992. (l) Taylor, J. G.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 857–869.

(13) (a) Schiemann, G.; Winkelmüller, W. *Org. Syntheses* **1943**, *2*, 299–302. (b) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572–1574. For an interesting alternative protocol, see: Schmidt, B.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2010**, *8*, 1406–1414.

(14) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079–2082.

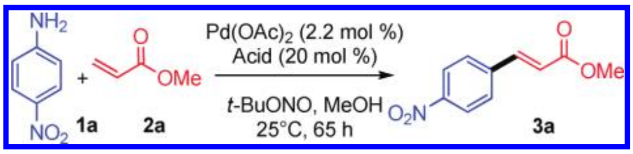
(15) (a) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2154–2158. (b) Pla-Quintana, A.; Roglans, A. *ARKIVOC* **2005**, *ix*, 51–62.

Scheme 4. General Strategy for a Double Catalytic Cycle



to decompose, even violently sometimes! This instability has been ascribed to the high redox potential and a preference for a homolytic dediazonization pathway.[17] Our optimization studies started with the screening of a variety of acids (20 mol %) in order to evaluate the influence of the acidity and/or the nature of the counterion (Table 1). We selected $Pd(OAc)_2$ as the palladium source and methanol as solvent on the basis of our previous studies in the field.[18] To our great surprise the tetrafluoroborate anion (entries 1–2) was not the most effective counterion whatever the source of the acid (i.e., HBF_4 and $BF_3\cdot Et_2O$), although it has been the most used in the literature. Phosphoric, sulfuric and carboxylic acids were also useless acids for this transformation (entries 3–6). Fortunately, we observed that sulfonic acids were very efficient at only 25 °C, whatever their structure (entries 7–10). Finally, we selected $MeSO_3H$ as the acid of choice for our further studies since it is the less expensive sulfonic acid commercially available, and it can be easily recovered by distillation at the end of the reaction. The acid loading could be lowered to 10 mol %; in that case, however, higher reaction times were required. We also screened a variety of additives to evaluate their impact on the reaction outcome. After considerable experimentations, we found that almost a quantitative yield can be reached by using anisole as additive (entry 10).

Table 1. Screening of Various Acids



entry	acid	yield (%)[a]
1	$BF_3\cdot Et_20$	60
2	HBF_4	47
3	Diphenylphosphate	20
4	H_3PO_4	12
5	H_2SO_4	54
6	CH_3CO_2H	13
7	*p*-Toluenesulfonic acid	87
8	Camphorsulfonic acid	90
9	$MeSO_3H$	84
10[b]	$MeSO_3H$	97

[a] Yields of isolated products. [b] Anisole (0.5 equiv) was used as additive.

Having an optimized protocol in hand, we first screened a variety of nitro-substituted anilines for reaction with methyl acrylate (Table 2). As already outlined, we selected nitro-based anilines due to the reluctance of the corresponding diazonium salts to achieve Heck–Matsuda coupling. Moreover, we also kept in mind that 2-nitrophenyl acrylates can be further transformed into heterocycles following our Heck-Reduction-Cyclization (HRC) strategy.[19] To our great pleasure, we observed that, in many cases, anisole can be omitted. All type of nitro-substituted anilines, bearing electron-poor or electron-rich functional groups, gave indifferently high yields of the corresponding cross-coupled products (entries 1–8). We also observed that ortho-substituted anilines were efficiently reacted with methyl acrylate (entries 3–11). These results are of importance since, in palladium chemistry, diazonium salts are frequently sensitive to steric hindrance. As a consequence, ortho-substituted partners often failed to give high yields of coupled products.

We also successfully screened anilines that do not bear a nitro group (entries 9–12). As of particular note is the perfect chemoselectivity at the diazonium functionality as leaving group when bromo-substituted anilines are involved in the Heck coupling (entries 8–9). This feature opens opportunities for further selective functionalization at the bromo group, especially with palladium-based chemistry.[20] The lower yield obtained with 2-methyl aniline is not yet fully understood, but volatility of the corresponding coupling product renders difficult the purification step (entry 10). Considering the role of anisole, we assume that it plays a

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(16) (a) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31–36. (b) Sengupta, S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1943–1944. (c) Priego, J.; Carretero, J. C. *Synlett* **1999**, 1603–1605. (d) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.* **2006**, *47*, 1325–1328.

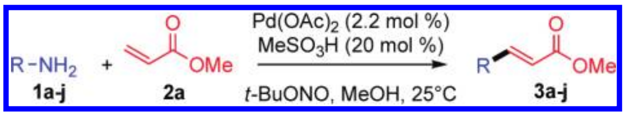
(17) Yasui, S.; Fujii, M.; Kawano, C.; Nishimura, Y.; Shioji, K.; Ohno, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 177–183.

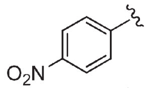
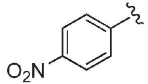
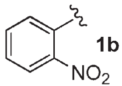
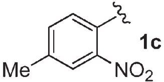
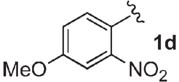
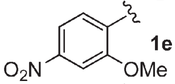
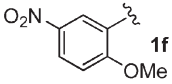
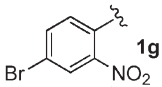
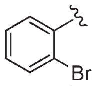
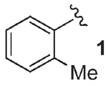
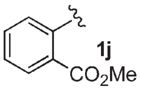
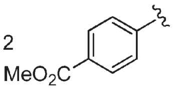
(18) (a) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2008**, *350*, 2559–2565. (b) Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem.—Eur. J.* **2010**, *16*, 5191–5204.

(19) (a) Felpin, F.-X.; Ibarguren, O.; Nassar-Hardy, L.; Fouquet, E. *J. Org. Chem.* **2009**, *74*, 1349–1352. (b) Felpin, F.-X.; Coste, J.; Zakri, C.; Fouquet, E. *Chem.—Eur. J.* **2009**, *15*, 7238–7245. (c) Ibarguren, O.; Zakri, C.; Fouquet, E.; Felpin, F.-X. *Tetrahedron Lett.* **2009**, *50*, 5071–5074. (d) Laudien, J.; Fouquet, E.; Zakri, C.; Felpin, F.-X. *Synlett* **2010**, 1539–1543.

(20) Taylor, R. H.; Felpin, F.-X. *Org. Lett.* **2007**, *9*, 2911–2914.

Table 2. Scope of the Reaction



entry	R =	anisole (equiv.)	time (h)	product	yield (%)[a]
1	 **1a**	0.5	48	**3a**	97
2	 **1a**	--	65	**3a**	84
3	 **1b**	--	65	**3b**	98
4	 **1c**	--	65	**3c**	97
5	 **1d**	--	48	**3d**	96
6	 **1e**	--	65	**3e**	99
7	 **1f**	--	48	**3f**	96
8	 **1g**	--	65	**3g**	98
9[b]	 **1h**	0.5	65	**3h**	74
10	 **1i**	0.5	65	**3i**	51
11	 **1j**	--	48	**3j**	99
12	 **1k**	0.5	48	**3k**	97

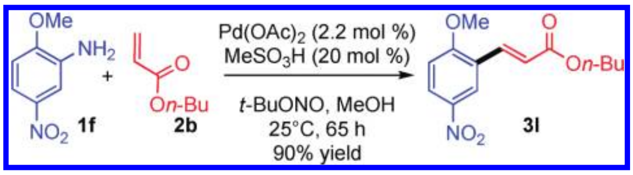
[a] Yields of isolated products. [b] Pd(OAc)$_2$ (4.4 mol %) was used.

crucial role in stabilizing palladium species and especially cationic intermediates involved in the catalytic cycle.

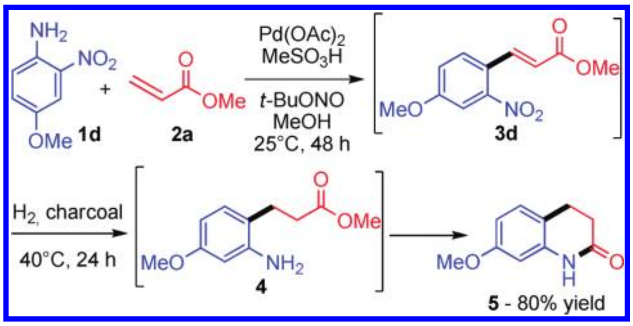
The extremely mild conditions developed with this protocol allowed the participation of other alkyl acrylates with negligible solvent-induced transesterification byproduct. For instance, butyl acrylate **2b** could be coupled with aniline **1f** with high yield (90%) without any base (Scheme 5).

The synthetic usefulness of our methodology can be extended to the facile preparation of quinolones following our recently developed HRC strategy (Scheme 6).[19b] For instance, the Heck coupling of aniline **1d** with methyl acrylate **2a**, followed by the in situ Pd-mediated reductions of the nitro group and the double bond, furnished intermediate **4** which spontaneously cyclized into the corresponding quinolone **5** with an overall 80% yield.

Scheme 5. Coupling with Butyl Acrylate



Scheme 6. Synthesis of Quinolone **5** by the HRC Strategy



In summary, we have described the first Heck–Matsuda reaction using a substoichiometric amount of diazonium salt through an uncovered double catalytic cycle. Our protocol features very mild conditions, and generates only environmentally benign byproduct such as t-BuOH, H$_2$O, and N$_2$. From a safety point of view, our approach does not require the isolation of hazardous aryl diazonium salts as they are in situ catalytically generated throughout the reaction advancement from the corresponding anilines.[21] Although we are still working on the improvement of the turnover number and the turnover frequency of our protocol, we have validated the challenging proof-of-concept stage. We believe that such a simple and safe methodology would initiate a growing interest for the chemistry of diazonium salts. Further developments in this area are actively pursued in our laboratory and will be reported in due course.

Acknowledgment. We gratefully acknowledge the “Université de Bordeaux”, the “Centre National de la Recherche Scientifique (CNRS)”, and the “Agence Nationale de la Recherche” (ANR JCJC 7141) for the financial support to this project. Dr. Karinne Miqueu and Dr. Jean-Marc Sotiropoulos (Université de Pau et des Pays de l’Adour) are acknowledged for fruitful discussions.

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

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(21) We believe that our procedure is safer because it does not require the use of isolated diazonium salts. Moreover, diazonium salts cannot accumulate in solution since it is formed through the generation of MeSO$_3$H as observed by ^{1}H NMR. We have performed the reaction up to 10 mmol without any noticeable problems. However, caution is warranted when working and handling such intermediates.