Organic LETTERS

Letter

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Hydrogen Peroxide Promoted Mizoroki–Heck Reactions of Phenyldiazenes with Acrylates, Acrylamides, and Styrenes

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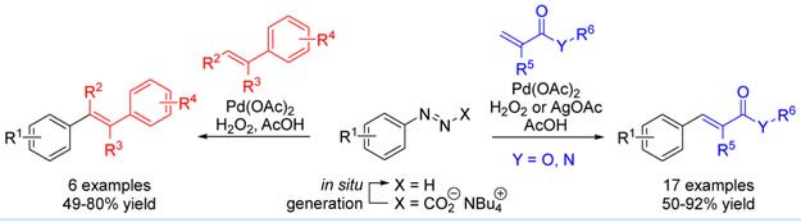
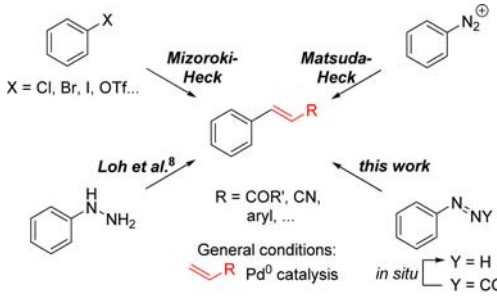
Supporting Information



ABSTRACT: Mizoroki–Heck reactions, which are well-known for aryldiazonium salts and which have recently been described for arylhydrazines, have now been extended to phenyldiazenes. In situ generation of phenyldiazenes from azocarboxylates allowed clean and selective reactions with styrenes, acrylates, and acrylamides using palladium(II) acetate in the presence of silver(I) acetate or hydrogen peroxide as oxidant. Hydrogen peroxide was thereby shown to be a cheap and broadly applicable alternative for the established palladium–silver(I) system.

Mizoroki–Heck[1] coupling reactions of aryl residues with alkenes have been known since 1971 and represent one of the most important palladium-catalyzed carbon–carbon bond-forming processes in the field of organic chemistry.[2,3] Besides commonly used aryl iodides, bromides, and chlorides, various other aryl precursors such as triflates,[4] diazonium salts,[5,6] boronic acids,[7] hydrazines,[8] and sulfonyl halides[9] have been employed (Scheme 1), and catalysts other than palladium have also been found useful.[7b,10] Among the aryl precursors, diazonium salts[5,6] have gained particular interest in a subtype which is generally referred to as the Matsuda–Heck reaction and which can often be conducted under comparably mild conditions.

Scheme 1. Mizoroki–Heck Reaction and Related Transformations: Nitrogen-Based Leaving Groups



The broad variety of studies on diazonium salts is therefore nicely complemented by recent work on arylhydrazines by Loh,[8] which showed that other aryl precursors may also enter the catalytic cycle in combination with a loss of dinitrogen. Interestingly, phenyldiazenes,[11] which represent the missing piece between aryldiazonium ions and hydrazines in terms of oxidation state, have not yet been described as precursors or intermediates in Heck reactions. Besides this formal gap to be closed, our interest in the role of phenyldiazenes in Heck-type reactions was due to successful trapping experiments of these often short-lived intermediates[12] and attractive future applications in ^{18}F-radiosynthesis, which would be enabled by the high-yielding access to ^{18}F-fluorophenylazocarboxylates.[13] Several series of preliminary experiments were carried out with phenylazocarboxylic acid *tert*-butyl esters[11,12] and methyl acrylate or styrene (see Tables S1–S8, Supporting Information). All variations, including solvents, bases, ligands, palladium sources, and various additives, did, however, give the desired cinnamic ester or stilbene only in yields lower than 46%. Whereas the change from *tert*-butyl to more reactive methyl azocarboxylates (see Table S9)[14] did not lead to significant improvements, a breakthrough could be achieved with phenylazocarboxylate salt **2a** in the presence of silver acetate in acetic acid (Table 1).[15] Under acidic conditions, phenylazocarboxylate salts are known to be converted to phenyldiazenes.[12] Preliminary experiments with **2a** were performed on a 0.175 mmol scale, and then optimization was continued on a 0.5 mmol scale (see Tables S10 and S11). Selected results from the final attempts with azocarboxylate **2a**, which was in all cases quantitatively obtained from the corresponding *tert*-butyl ester **1a**, are summarized in Table 1. Addition of triphenylphosphine to the standard reaction mixture led to a slight improvement (entries 1, 2), whereas a higher reaction temperature of 60 °C significantly decreased the

Received: February 16, 2016
Published: March 14, 2016

DOI: 10.1021/acs.orglett.6b00449
Org. Lett. 2016, 18, 1586–1589

Table 1. Optimization of Reaction Conditions

entry	variation of conditions[a]	yield[b] of **4aa** (%)
1		72
2	PPh_3 (10 mol %) added	75
3	reaction at 60 °C	53
4	H_2O_2 (2 equiv) instead of AgOAc	83
5	absence of Pd	0

[a]Reaction conditions: tetrabutylammonium hydroxide (0.75 mmol), **1a** (0.5 mmol), CH_3CN (1.4 mL), 5 min; then slow addition of **2a** (over 45 min) to **3a** (2.5 mmol), AgOAc (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), AcOH (3 mL), rt. [b]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

yield (entry 3). A screening of oxidants (see Table S12) with the aim of replacing silver acetate revealed hydrogen peroxide as most suitable reagent (entry 4).

To the best of our knowledge, hydrogen peroxide is known to be formed in oxidative Heck reactions[16] but has so far not been described as a cheap additive to promote such palladium-catalyzed carbon−carbon bond formations. A final experiment in the absence of palladium ruled out a mechanism via a free aryl radical, which could basically lead to the same product **4aa**.[17]

After the synthetic applicability of the reaction reported in Table 1 (entry 4) was demonstrated on a 3 mmol scale (86% yield), we started to determine scope and limitations. A first series of experiments was carried out with various substituents on the aromatic core of the azocarboxylic ester **1** (Table 2). Halogenated (entries 1−10) as well as most donor- and acceptor-substituted aryl residues (entries 11−14) were tolerated, with the strongly electron-donating dimethylamino group being the only exception (entry 15). A comparison of the known combination of palladium with silver acetate (method A)[15] with the new Pd/H_2O_2 system was carried out among the halogenated azo esters **1a**,**c**,**d**,**f**. Thus, only the reactions with the 4-iodo compound **1f** showed a certain preference for method A (entries 9 and 10). In the next step, variations of the alkene were investigated in combination with azocarboxylic esters **1a** and **1c** (Table 3). The azo esters **1a** and **1c** were chosen as both had given comparable yields in the previous study (Table 2) and the brominated compound would allow further substitution, whereas the fluorinated compound is useful to evaluate the applicability for ^{18}F-radiolabeling. Increased steric demand of the ester (entries 1−3) as well as additional substituents on the alkene (entries 4−6) were tolerated except for the α-substituted acrylate **3d** (entries 4 and 5), which preferably gave the isomeric acrylate **4ad′** (Figure 1) instead of the fully conjugated product **4ad**.[18] Experiments with acrylamides **3f** and **3g** led to the highest yields in this series (entries 7−9). Methyl vinyl ketone (**3i**) initially provided a mixture of the desired product **4ch** and its reduced analogue **4ch′** (entry 10, see also Figure 1). Through a replacement of acetic acid by formic acid with omission of the oxidant the product ratio could be fully shifted to **4ch′** (78%) (entry 11).[19]

Surprisingly, no conversion could be achieved in attempts with acrylonitrile, which has successfully been used in Heck reactions

Table 2. Evaluation of Substrate Scope and Limitations: Aromatic Substitution Pattern

entry	**1**: R^1 =	method[a,b]	yield[c] of **4** (%)
1	**1a**: 4-Br	A	**4aa** (75)
2	**1a**: 4-Br	B	**4aa** (80)
3	**1b**: 2-Br	B	**4ba** (60)
4	**1c**: 4-F	A	**4ca** (77)
5	**1c**: 4-F	B	**4ca** (73)
6	**1d**: 4-Cl	A	**4da** (75)
7	**1d**: 4-Cl	B	**4da** (78)
8	**1e**: 2,4-Cl_2	B	**4ea** (61)
9	**1f**: 4-I	A	**4fa** (48)
10	**1f**: 4-I	B	**4fa** (36)
11	**1g**: 4-CN	B	**4ga** (56)
12	**1h**: 4-NO_2	B	**4ha** (49)
13	**1i**: 4-OMe	B	**4ia** (56)
14	**1j**: 4-O(4-FC_6H_4)	B	**4ja** (88)
15	**1k**: 4-NMe_2	B	**4ka** (traces)

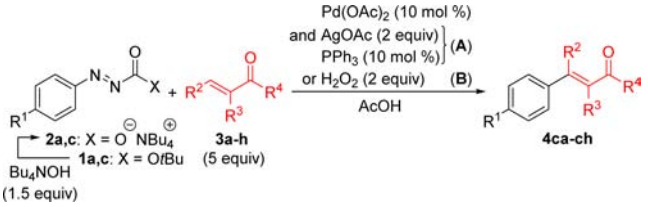
[a]Conditions A: tetrabutylammonium hydroxide (0.75 mmol), **1** (0.5 mmol), CH_3CN (1.4 mL), 5 min; then slow addition of **2** (over 45 min) to **3a** (2.5 mmol), AgOAc (1.0 mmol), PPh_3 (0.05 mmol), $Pd(OAc)_2$ (0.05 mmol), AcOH (3 mL), rt. [b]Conditions B: tetrabutylammonium hydroxide (0.75 mmol), **1** (0.5 mmol), CH_3CN (1.4 mL), 5 min; then slow addition of **2** (over 45 min) to **3a** (2.5 mmol), H_2O_2 (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), AcOH (3 mL), rt. [c]Yields after purification by column chromatography.

before.[20] A competition experiment with azo ester **1a** and equal amounts of methyl acrylate (**3a**) and acrylonitrile under conditions B provided only **4ca** (47%), thereby underlining the low reactivity of the nitrile. In the series of alkenes, **3d** (entries 4 and 5) and **3f** (entries 7 and 8) can be used to compare methods A and B, which did not show significant differences. In contrast to that, a comparison of methods A and B in reactions with styrene (**3i**) clearly demonstrated that only the conditions including hydrogen peroxide are suitable for this type of alkene (Table 4, entries 1 and 2). Whereas additional substituents on the aromatic core did not have much influence on the reaction (entries 3−5), the introduction of methyl groups on the double bond led to differentiated results, which are comparable to those obtained for acrylates **3d** and **3e** (cf., Table 3, entries 4−6). Likewise, methylation in the α-position provided an isomeric product **4dm′** (Table 4, entry 6, see also Figure 1) and methylation in the β-position was tolerated to give **4dn**, but at a below average yield of 49% (entry 7). Potential applicability in radiosynthesis was demonstrated in a reaction of the fluorinated azoester **1c** with styrene **3k** (entry 8).

A two-step sequence demonstrating the synthetic utility is shown in Scheme 2. Nucleophilic substitution of *N*-acetyl-L-tyrosine (**5**) with azo ester **1h** could be achieved at room temperature, and diphenyl ether **6** was then further converted under the new Heck-type conditions to give **7**. As known bifunctional 1,4-disubstituted benzenes do not allow such a sequence under comparably mild conditions,[21] Heck reactions of

DOI: 10.1021/acs.orglett.6b00449
Org. Lett. 2016, 18, 1586−1589

Table 3. Evaluation of Substrate Scope and Limitations: Acrylates, Acrylamides, and Methyl Vinyl Ketone



entry	**1**: R^1 =	**3**: R^2, R^3, R^4 =	method	yield[a,b] of **4** (%)
1	**1c**: F	**3a**: H, H, OMe	A	**4ca** (76)
2	**1a**: Br	**3b**: H, H, OEt	A	**4ab** (78)
3	**1c**: F	**3c**: H, H, O*t*Bu	A	**4cc** (77)
4	**1a**: Br	**3d**: H, Me, OMe	A	**4ad** (13)[c]
				4ad′ (42)[c]
5	**1a**: Br	**3d**: H, Me, OMe	B	**4ad** (15)
				4ad′ (50)
6	**1c**: F	**3e**: Me, H, OMe	B	**4ce** (68)
7	**1c**: F	**3f**: H, H, NH_2	A	**4cf** (87)
8	**1c**: F	**3f**: H, H, NH_2	B	**4cf** (83)
9	**1a**: Br	**3g**: H, H, NHC_4H_9	B	**4ag** (92)
10	**1c**: F	**3h**: H, H, Me	B	**4ch** (34)
				4ch′ (48)
11	**1c**: F	**3h**: H, H, Me	B[d]	**4ch′** (78)

[a]For conditions A and B, see footnotes of Table 2. [b]Yields after purification by column chromatography. [c]Not isolated. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [d]Reaction in HCOOH in the absence of H_2O_2.

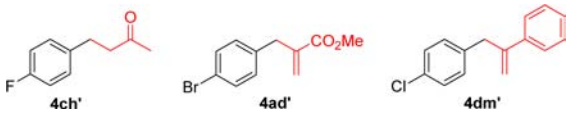
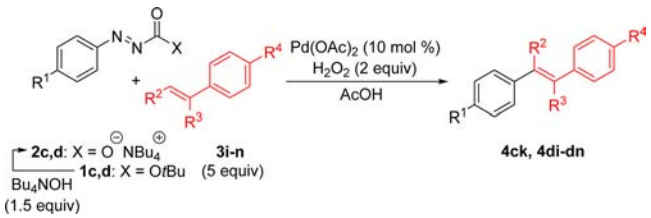


Figure 1. Additional products.

Table 4. Evaluation of Substrate Scope and Limitations: Styrenes

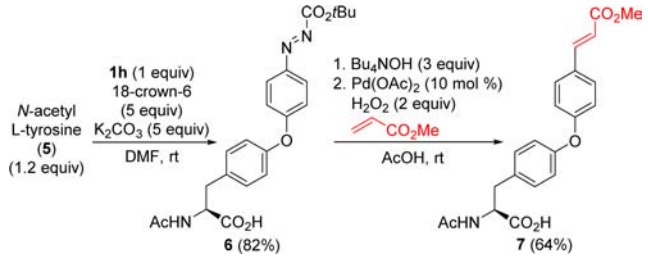


entry	**1**: R^1 =	**3**: R^2, R^3, R^4 =	method	yield[a,b] of **4** (%)
1	**1d**: Cl	**3i**: H, H, H	A	**4di** (0)
2	**1d**: Cl	**3i**: H, H, H	B	**4di** (71)
3	**1d**: Cl	**3j**: H, H, F	B	**4dj** (70)[c]
4	**1d**: Cl	**3k**: H, H, Cl	B	**4dk** (80)
5	**1d**: Cl	**3l**: H, H, CN	B	**4dl** (61)
6	**1d**: Cl	**3m**: H, Me, H	B	**4dm** (−)
				4dm′ (14)
7	**1d**: Cl	**3n**: Me, H, H	B	**4dn** (49)
8	**1c**: F	**3k**: H, H, Cl	B	**4ck** (73)[c]

[a]For conditions A and B, see footnotes of Table 2. [b]Yields after purification by column chromatography. [c]Compounds **4dj** and **4ck** are identical.

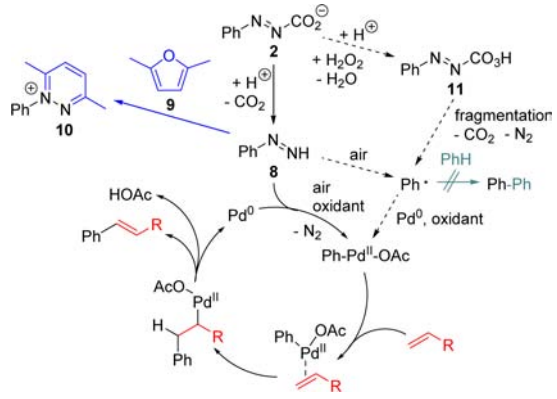
phenylazocarboxylates via phenyldiazenes could become valuable tools for the broad functionalization of peptides.

Scheme 2. Two-Step Functionalization of *N*-Acetyl-L-tyrosine



A plausible reaction mechanism is depicted in Scheme 3. The intermediacy of phenyldiazene **8**, which is formed under acidic

Scheme 3. Plausible Reaction Mechanism and Trapping Experiments



conditions from azocarboxylate **2**,[22] was proven in a trapping experiment[12] with 2,5-dimethylfuran (**9**) yielding a pyridazinium salt **10** (see the Supporting Information). Although all reactions were conducted under air,[23] which usually induces a quick decay of phenyldiazenes[24] into aryl radicals, no biphenyls were found in a test reaction containing a large excess of benzene. We therefore assume that phenyldiazene **8** can directly enter the catalytic cycle.[25,26] For hydrogen peroxide mediated reactions, an alternative pathway via fragmentation of azo peracid **11** can currently not be excluded.[27] This pathway would circumvent the intermediacy of diazene **8**.

After entering the cycle, the oxidants silver(I) acetate and hydrogen peroxide are likely to ensure an adjustment of the oxidation state of the palladium complex, which is necessary since the oxidation state of phenyldiazene is one level lower than that of a diazonium ion, which can be used in Heck reactions without additional oxidant. The oxidation by hydrogen peroxide appears to be much faster than by silver(I) ions, since the peroxide (method B) tolerates a fast addition of azocarboxylate **2** to the reaction mixture (64% of **4aa**, cf. entry 2, Table 2; see also the Supporting Information), whereas a similar modification of method A led to a complex product mixture. Whether this oxidation step occurs before, as assumed in Scheme 3, or after coordination of the Pd complex to the alkene is currently difficult to assess. In this context, the unprecedented selectivity to acrylic esters over acrylonitrile[20] may point to coordination of a Pd^I rather than a Pd^{II} species to the alkene. The fact that isomeric product mixtures were obtained from reactions with 2-methacrylic acid methyl ester (**3d**) (Table 3, entries 4 and 5), as has been observed under classical reaction conditions,[18a,b]

DOI: 10.1021/acs.orglett.6b00449
Org. Lett. 2016, 18, 1586−1589

supports the assumption that the late stages of the mechanism are identical to those of common Heck reactions.

In summary, a new version of the Mizoroki−Heck reaction proceeding via phenyldiazenes has been developed. Representing the missing piece between known reactions of arylhydrazines and aryldiazonium ions, it is useful to convert a broad variety of olefinic substrates under very mild conditions at room temperature and under air with full *E*/*Z* selectivity. Beneficially, cheap H_2O_2 can be used as oxidant, which is so far unknown in palladium-catalyzed C−C bond formations. Ongoing research is directed toward further applications of the Pd−H_2O_2 system including combinatorial chemistry and radiochemical reactions based on readily available [^{18}F]-4-fluorophenylazocarboxylic acid *tert*-butyl ester ([^{18}**F**]-**1c**).[13]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00449.

General experimental methods, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (GRK 1910, "Medicinal Chemistry of Selective GPCR Ligands", subproject B3 and HE5413/3-3). We thank Daniel Thon (Pharmaceutical Chemistry, FAU Erlangen-Nürnberg) for experimental assistance.

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(25) Alternatively, one may assume a very fast addition of aryl radicals to the Pd complex. For a related work, see: Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205.

(26) For related studies and the "complex interactions that occur in the coordination sphere of palladium during the Heck reaction with arenediazonium salt", see: Sabino, A. A.; Machado, A. H. L.; Correia, R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514.

(27) (a) Groves, J. T.; Van der Puy, M. *J. Am. Chem. Soc.* **1975**, *97*, 7118. (b) See also the Supporting Information (Scheme S3).

DOI: 10.1021/acs.orglett.6b00449
Org. Lett. 2016, 18, 1586−1589