Palladium-Catalyzed Coupling of Pyrid-4-yl Nonaflates with Methyl Diazoacetate

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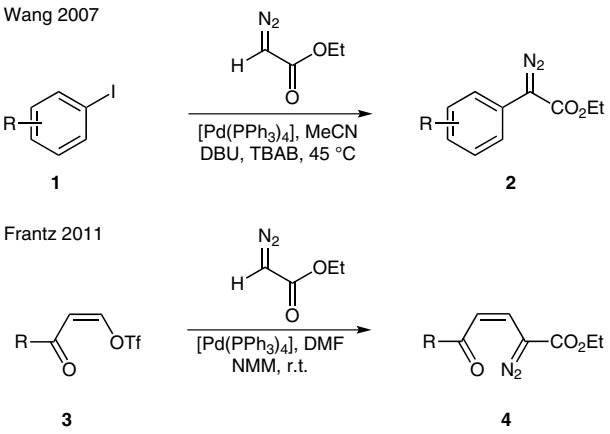
Received: 16.04.2012; Accepted: 03.05.2012

Abstract: Palladium-catalyzed couplings of pyrid-4-yl nonaflates with methyl diazoacetate are described. After optimization of the reaction conditions the scope of the transformation proved to be fairly broad and a series of pyrid-4-yl-substituted methyl diazoacetates was prepared in generally high yields.

Key words: pyridines, bipyridines, nonaflates, palladium catalysis, cross couplings, diazoacetate

Palladium-catalyzed coupling reactions have evolved into one of the most efficient methods for the construction of C–C bonds.[1] Coupling between aryl halides and metal-organic species have been well-established for many years. In contrast, palladium-catalyzed couplings employing CH-active precursors as carbon nucleophiles have only recently been developed. Based on the pioneering work of Hartwig and Buchwald on the intermolecular coupling of enolates derived from ketones, esters and amides,[2] the use of other CH-acidic compounds such as nitriles, nitroalkanes, aldehydes etc. has attracted growing interest in palladium-catalyzed arylation processes over the last years.[3] Recently, two reports have been published describing the use of alkyl diazoacetates as coupling partners: Wang and co-workers developed a protocol for the palladium-catalyzed coupling of vinyl and aryl iodides with ethyl diazoacetate to compounds **2**,[4] and Frantz et al. reported the coupling of acceptor-substituted enol triflates[5] providing products such as **4** (Scheme 1).

Over the last years we have systematically investigated the behavior of pyrid-4-yl nonaflates in various cross-coupling processes.[6] Intrigued by the reports of the two groups mentioned above, we wanted to identify reaction conditions for palladium-catalyzed couplings of pyrid-4-yl nonaflates with alkyl diazoacetates, which should lead to structurally interesting new pyrid-4-yl diazoacetates. Only a few reports describe the preparation and use of pyridyl diazoacetates, and the majority of the synthetic routes are based on diazo group transfer processes employing pyrid-4-yl acetates as starting materials.[7] Hence, the palladium-catalyzed coupling between pyrid-4-yl nonaflates and alkyl diazoacetates would present a useful and flexible alternative to access these versatile compounds.

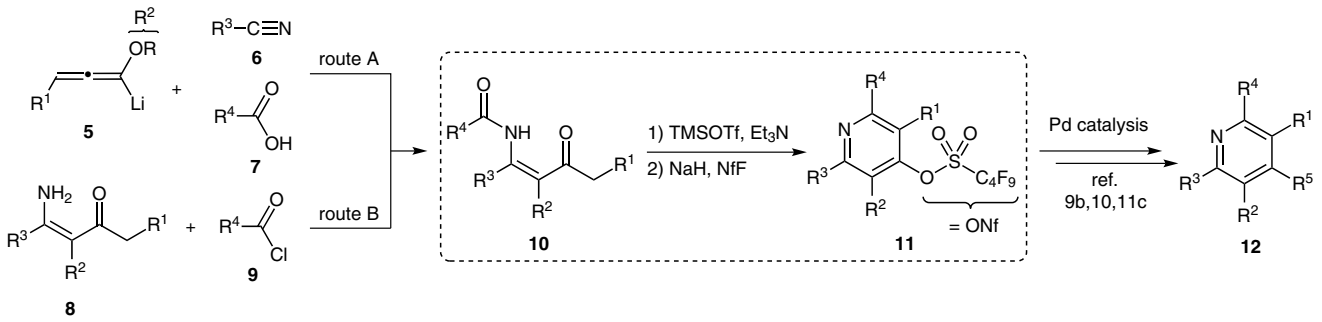


Scheme 1 Literature examples for the palladium-catalyzed coupling of ethyl diazoacetate with aryl iodides and electron-deficient alkenyl triflates

As we demonstrated earlier, pyrid-4-yl nonaflates **11** can be prepared through a simple two-step process utilizing a TMSOTf-promoted cyclocondensation of β-ketoenamides **10** followed by a nonaflation step with the intermediate 4-hydroxypyridines (Scheme 2).[8] Two routes have been developed for the preparation of the required β-ketoenamides: a multi-component approach based on the reaction of lithiated alkoxyallenes **5**, nitriles **6**, and carboxylic acids **7** (Scheme 2, route A)[9] or the acylation of simple enaminoketones **8** with acyl chlorides **9** (route B).[10] In addition to a series of highly substituted pyridine derivatives, we also prepared enantiopure pyridine derivatives with side chains bearing stereogenic centers in the 2- and/or 6-position.[11] Some of these new pyridines proved to be good ligands for asymmetric transformations, including the addition of zinc organyls to aldehydes or the iridium-catalyzed hydrogenation of olefins.[12]

As we had large quantities of the enantiopure pyridyl nonaflate **13a** available from a previous investigation, we decided to use this compound in our optimization studies. In a first experiment, **13a** was reacted with methyl diazoacetate under reaction conditions similar to those reported by Frantz and co-workers[5] (Table 1, entry 1). Although the desired product **14a** could be isolated, the yield was only moderate and the reaction was rather slow. Even after three days at room temperature, complete conversion was not achieved. Unfortunately, neither higher reaction temperatures nor changes in the stoichiometry of the reagents led to higher conversions.

SYNLETT 2012, 23, 1670–1674
Advanced online publication: 14.06.2012
DOI: 10.1055/s-0031-1290398; Art ID: ST-2012-D0334-L



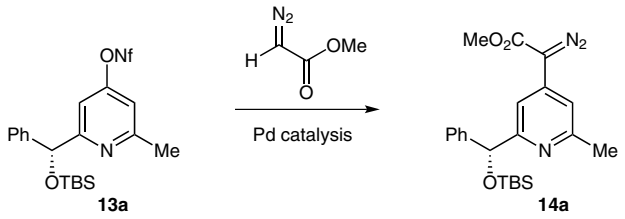
Scheme 2 Synthesis of highly substituted pyrid-4-yl nonaflates **11** by TMSOTf/base-promoted cyclocondensations of β-ketoenamides **10** followed by nonaflations and palladium-catalyzed transformations of **11** leading to specifically substituted pyridine derivatives **12**

We next applied the reaction conditions reported by Wang and co-workers.[4] Although this led to complete conversion of pyridyl nonaflate **13a** within 24 hours, the yield of the isolated coupling product **14a** was only slightly improved (Table 1, entry 2).

To identify the origin of the observed higher reaction rates under Wang's conditions, a systematic screening was undertaken in which all parameters were varied. We found that the use of TBAB as an additive – in contrast to the coupling of aryl iodides – had no significant influence on the reaction efficiency (compare Table 1, entries 2 and 3). However, both the base and the solvent seem to strongly influence the reaction efficacy. The use of *N*-methylmorpholine (NMM) instead of DBU led to significantly diminished yields and a change of the solvent from acetonitrile to DMF proved to have an even more deleterious effect, leading to a low yield of 22% (Table 1, entries 4 and 5). By screening different amine bases, we found that triethylamine gave the best results; 72% of the desired coupling product **14a** could be isolated after only four hours reaction time (Table 1, entry 6). Unexpectedly, the use of Hünig's base gave a dramatically lower yield (Table 1, entry 7). We also tested whether other palladium catalysts were capable of promoting the coupling reaction, but neither $[Pd_2(dba)_3]/P(t\text{-}Bu)_3$ nor $[PdCl_2(PPh)_3]$ afforded product **14a** (Table 1, entries 8 and 9). Finally, in the absence of any palladium catalyst no product formation was observed, ruling out a competitive addition–elimination process (Table 1, entry 10).

With the optimized reaction conditions (Table 1, entry 6),[13] we then started to evaluate the substrate scope of the process with respect to different substitution patterns at

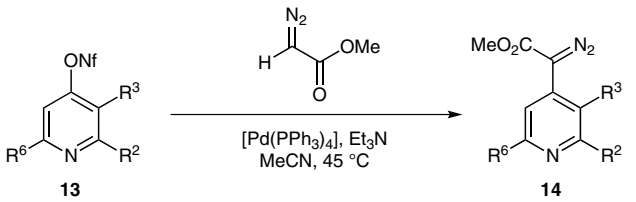
Table 1 Optimization of the Palladium-Catalyzed Coupling of Methyl Diazoacetate with Pyrid-4-yl Nonaflate **13a**

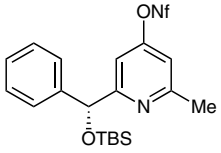
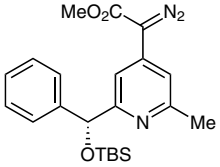
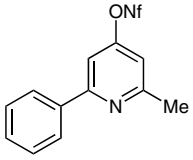
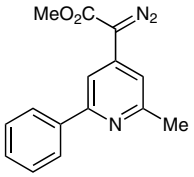
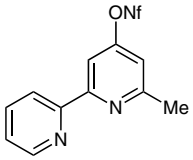
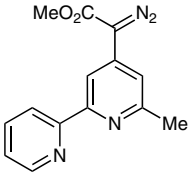
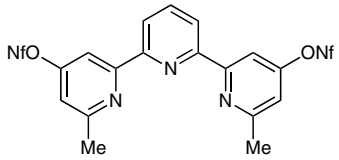
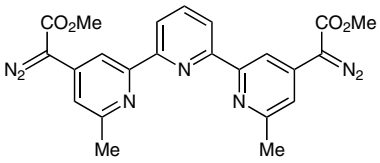
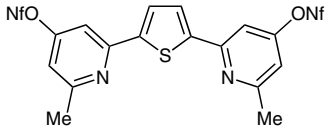
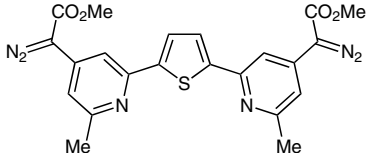
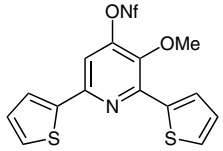
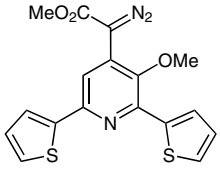
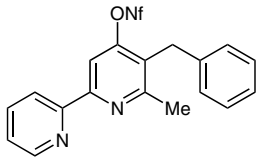
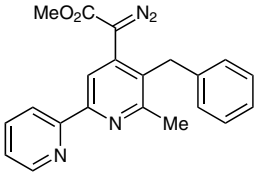


Entry	Catalyst	Conditions[a]	Time (h)	Yield (%)
1	$Pd(PPh_3)_4$ (5 mol%)	NMM, DMF, r.t.	72	44[b]
2	$Pd(PPh_3)_4$ (10 mol%)	DBU, MeCN, TBAB, 45 °C	24	49
3	$Pd(PPh_3)_4$ (10 mol%)	DBU, MeCN, 45 °C	24	45
4	$Pd(PPh_3)_4$ (10 mol%)	NMM, MeCN, 45 °C	24	35
5	$Pd(PPh_3)_4$ (10 mol%)	DBU, DMF, 45 °C	24	22
6	$Pd(PPh_3)_4$ (10 mol%)	Et_3N, MeCN, 45 °C	4	72
7	$Pd(PPh_3)_4$ (10 mol%)	$(i\text{Pr})_2$NEt, MeCN, 45 °C	24	8
8	$Pd_2(dba)_3$ (5 mol%)	$[HP(t\text{-}Bu)_3][BF_4]$ (10 mol%) NMM, DMF, r.t.	24	–
9	$PdCl_2(PPh_3)_2$ (5 mol%)	Et_3N, MeCN, 45 °C	24	–
10	No catalyst	DBU, MeCN, 45 °C	24	–

[a] NMM = *N*-methylmorpholine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAB = tetra-*n*-butylammonium bromide.
[b] Complete conversion was not achieved.

Table 2 Substrate Scope of the Palladium-Catalyzed Coupling of Pyrid-4-yl Nonaflates **13** with Methyl Diazoacetate



Entry	Pyrid-4-yl Nonaflate		Product		Time (h)	Yield (%)
1[a]		**13a**		**14a**	4	72
2[b]		**13b**		**14b**	1.5	84
3[c]		**13c**		**14c**	1.5	87
4[a]		**13d**		**14d**	1	93
5[a]		**13e**		**14e**	1	77
6[a]		**13f**		**14f**	72	28 (53)[d]
7[c]		**13g**		**14g**	96	37 (81)[d]

[a] $Pd(PPh_3)_4$ (10 mol%) was used.
[b] $Pd(PPh_3)_4$ (5 mol%) was used.
[c] $Pd(PPh_3)_4$ (7 mol%) was used.
[d] Yield based on recovered starting material given in parenthesis.

the pyridine ring; the results are summarized in Table 2. Regardless of the electronic nature of the pyridine ring substituents, the coupling reactions were complete within a few hours (typically within 1–4 h) and good yields were obtained (Table 2, entries 1–5). Substituents in the 3-position, however, seem to have a significant impact on the reaction efficacy. Hence, 3-methoxy-2,6-(dithienyl)pyrid-4-yl nonaflate (**13f**) and 3-benzyl-substituted pyridine derivative **13g** were transformed at significantly lower rates than all other substrates tested, and full conversions into the corresponding pyrid-4-yl methyl diazoacetates were not achieved within three days reaction time (Table 2, entries 6 and 7); considerable amounts of starting material were isolated in these experiments. Apart from this limitation, the developed conditions proved to be rather general and it could be shown that alkyl, aryl, and heteroaryl substituents in the 2- or 6-position of the pyridine ring were well-tolerated (Table 2, entries 2–5).

Remarkably, the preparation of 2,2′-bipyridine and 2,2′:6′,2″-terpyridine derivatives **14c** and **14d** could also be achieved in excellent yields (Table 2, entries 3 and 4). The twofold coupling required for the conversion of **13d** into bis(diazo) compound **14d** proceeded with particularly high efficacy. An additional practical aspect of the developed reaction conditions is the fact that, in some cases, the generated pyrid-4-yl-substituted methyl diazoacetates directly precipitate from the reaction mixture. Thus, compounds **14d** and **14e** could be isolated in analytical pure form upon simple filtration. In addition, as already shown in the optimization studies, TBS-protected hydroxymethyl-substituted pyridyl nonaflates can be coupled without touching the functionalized sidechain. The high yield of thienyl-substituted compound **14e** (Table 2, entry 5) demonstrates that the presence of a sulfur-containing group does not hamper the coupling step.

We also briefly examined other aryl and alkenyl nonaflates. Interestingly, neither phenyl nonaflate nor (*Z*)-pent-1-en-1-yl nonaflate[14] were transformed into the corresponding diazo compounds under the developed reaction conditions. Apparently, only nonaflates containing electron-deficient substituents are able to undergo the palladium-catalyzed coupling with methyl diazoacetate, which is in agreement with results obtained by Frantz and coworkers[5] regarding alkenyl triflates.

In conclusion, we have established an efficient method for the preparation of pyrid-4-yl-substituted methyl diazoacetates **14** based on palladium-catalyzed couplings of pyrid-4-yl nonaflates **13** with methyl diazoacetate. Diazoalkanes of type **14** are interesting compounds that could undergo a multitude of subsequent reactions such as 1,3-dipolar cycloadditions or processes involving carbenes.[15] Application of a pyrid-4-yl alkyl diazoacetate in surface modification processes has already been described.[16] The method reported here may also find use in the synthesis of other new heteroaryl-substituted alkyl diazoacetates.

Acknowledgment

The authors thank the Studienstiftung des Deutschen Volkes (PhD fellowship to C.E.), the Deutsche Forschungsgemeinschaft (GK 1582) and Bayer Healthcare for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Palladium-Catalyzed Coupling of Pyrid-4-yl Nonaflates with Methyl Diazoacetate; Typical Procedure for 14a**: A sealed tube equipped with a stirring bar was charged with $Pd(PPh_3)_4$ (40 mg, 0.034 mmol) and pyrid-4-yl nonaflate **13a**[11c] (210 mg, 0.34 mmol). MeCN (3.5 mL), Et_3N (71 μL, 0.51 mmol) and methyl diazoacetate (100 mg, 1.00 mmol) were added and the resulting solution was stirred at 45 °C for 4 h until complete conversion of the starting material was observed (reaction monitored by TLC). H_2O (20 mL) and EtOAc (20 mL) were added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane–EtOAc, 4:1) to provide pyridyl diazoacetate **14a** (101 mg, 72%) as a yellow oil. $[\alpha]_D$ –63.5 (*c* = 1.0, $CHCl_3$). IR (ATR): 3090–2860 (C-H), 2095 (CN_2), 1715 (C=O), 1595–1550 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.00, 0.93 (2 × s, 6 H + 9 H, OTBS), 2.49 (s, 3 H, Me), 3.86 (s, 3 H, CO_2CH_3), 5.83 (s, 1 H, C*H*Ph), 7.17–7.20, 7.25–7.29, 7.37–7.38, 7.47–7.49 (4 × m, 1 H + 3 H + 1 H + 2 H, Ph, 3-H/5-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.93, –4.91, 18.2, 25.7 (2 × q + s + q, OTBS), 24.6 (q, Me), 52.1 (q, CO_2CH_3), 77.5 (d, C*H*Ph), 110.3, 115.5 (2 × d, C-3/C-5), 126.2, 127.0, 128.0 (3 × d, Ph), 128.2, 136.0, 143.7, 157.6 (4 × s, Ph, C-2/C-4/C-5), 164.3 (s, CO); the signal for $C=N_2$ was not detected. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd. for $C_{22}H_{30}N_3O_3Si$: 412.2051; found: 412.2039.

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