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Full Paper

$Mo(CO)_6$ as a Solid CO Source in the Synthesis of Aryl/Heteroaryl Weinreb Amides under Microwave-Enhanced Condition

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The facile transformation of aryl/heteroaryl nonaflates into corresponding amides via Pd-catalyzed aminocarbonylation using $Mo(CO)_6$ as a solid CO source under microwave-enhanced condition is reported. The method was found to be tolerant with respect to a diverse range of electronically biased aryl/heteroaryl nonaflates, and exceptional yields were obtained. The optimized protocol was further extended to a diverse range of amines.

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Introduction

The development of efficient synthetic methods that would allow access to a wide range of synthetically viable intermediates continues to be a key area of research in chemistry. Among these methods, palladium-catalyzed cross-coupling reactions have been considered as the most reliable synthetic technique for achieving these objectives. Palladium-catalyzed C–C and C–N bond-forming reactions have gained tremendous potentials in both academia and industry.[1–9] Ever since the discovery of Pd-catalyzed three-component reaction by Heck and Schoenberg[10] in 1974, considerable efforts have been made by various researchers across the globe in improving its synthetic applicability by developing efficient catalytic systems.[11–16] The amide functionality being an important fragment in plastics, detergents, lubricants, as well as in many biologically relevant molecules; thus, robust synthetic methods that would allow access to these analogues are highly desirable.

The use of aryl/heteroaryl halides (I, Br, Cl) in aminocarbonylation reactions has been well documented in literature.[17–33] Activated aryl/heteroaryl chlorides were also found to be efficient synthons in this transformation.[34,35] Efforts in using pseudo halide (e.g. triflate (Tf), tosylate (Ts), mesylate (Ms)) have expanded the substrate scope for this transformation.[36–39] As demonstrated in the literature, aryl/heteroaryl triflates are reactive; however, the stability concerns associated with this pseudo halide open the room for developing a highly reactive and stable counterpart that can

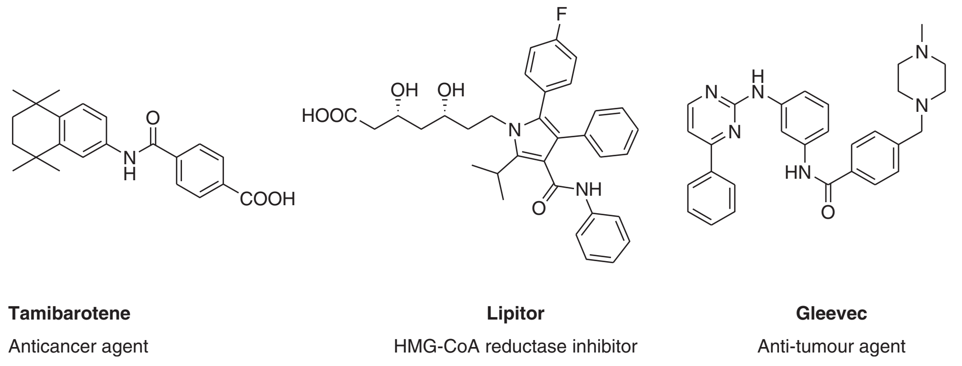
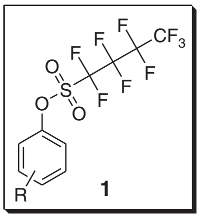


Fig. 1. Biologically relevant amide containing pharmaceuticals.



Nf = $-SO_2(CF_2)_3-CF_3$; R = alkyl, alkoxy, halo, cyano, nitro, ester, etc.

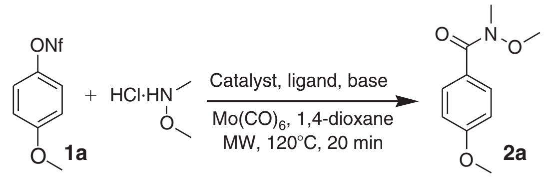
Chart 1. Synthesis of aryl/heteroaryl nonaflates.

influence these transformations more efficiently. Aryl tosylates and mesylates, though found to be attractive, are often problematic cross-coupling substrates in palladium-catalyzed reactions owing to their high reluctance towards oxidative addition. Fig. 1 shows biologically relevant amide-containing pharmaceuticals.

Result and Discussion

As a part of our research program on palladium-mediated cross-coupling reactions,[11–16] we were interested in the use of aryl/heteroaryl nonaflate as an efficient and stable pseudo halide in aminocarbonylation reaction. Beller et al. reported the in situ generation of aryl nonaflates from corresponding phenols and their subsequent conversion into benzamides under palladium-catalyzed condition.[40] The use of this pseudo halide in other cross-coupling reactions is also well studied and documented in literature.[41–43] The excellent stability and high reactivity of this electrophile compared with that of other pseudo halides prompted us to explore its synthetic utility in aminocarbonylation. In most of the protocols, a high gaseous CO pressure, long reaction times, and high temperatures are essential to drive the reaction to success.[44–48] In this paper, we report the use of $Mo(CO)_6$ as a solid CO-releasing agent in the aminocarbonylation reactions of aryl/heteroaryl nonaflates (Tables 2, 4) under microwave-assisted condition.

Table 1. Optimization of the reaction conditions[A,B]



Entry	Catalyst [mol-%], ligand [mol-%]	Base	Yield [%]
1	$Pd(OAc)_2$ (2), PPh_3 (4)	DBU	20
2	$Pd(OAc)_2$ (2), SPhos (4)	DBU	55
3	$Pd(OAc)_2$ (2), (*S*)-BINAP (4)	DBU	50
4	$Pd(OAc)_2$ (2), dppp (4)	DBU	65
5	$Pd(OAc)_2$ (2), dppb (4)	DBU	82
6	$Pd(OAc)_2$ (2), dppf (4)	DBU	61
7	$Pd(OAc)_2$ (2), DPEphos (4)	DBU	59
8	$Pd(OAc)_2$ (2), xantphos (4)	DBU	87
9	$Pd(OAc)_2$ (2), xantphos (4)	DABCO	65
10	$Pd(OAc)_2$ (2), xantphos (4)	TEA	30

[A] Optimized reaction conditions performed at 5-g scale (Table 1, entry 8): nonaflate (250 mg, 1 equiv.), amine (1.0 equiv.), base (3 equiv.), Pd catalyst (0.02 equiv.), ligand (0.04 equiv.), $Mo(CO)_6$ (0.35 equiv.), 1,4-dioxane, 120°C, microwave (MW) irradiation for 20 min.

[B] Abbreviations: PPh_3, triphenyl phosphine; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; BINAP,(S)-(−)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine); dppb, 1,4-Bis(diphenylphosphino)butane; dppf, 1,1′-Bis(diphenylphosphino)ferrocene; DPEphos, (Oxydi-2,1-phenylene)bis(diphenylphosphine); DBU, 1,8-diazabicycloundec-7-ene; DABCO, 1,4-diazabicyclo[2.2.2]octane; TEA, triethylamine

Guided by our previous results,[49,50] we anticipated that the types of catalyst, solvent, and ligand would have crucial influence on the reactivity. In the present study, a wide range of activated and deactivated aryl/heteroaryl nonaflates were synthesized from corresponding phenols (Chart 1).

These electrophilic intermediates were found to have excellent shelf life and can be stored under usual laboratory conditions for long periods of time. Literature studies indicate that electrophiles containing an electron-donating group (deactivated system)

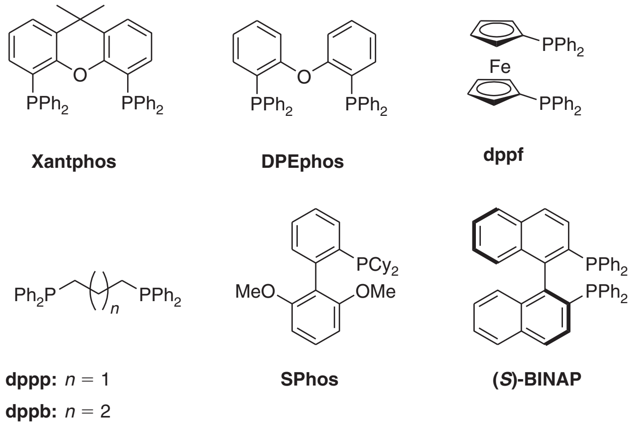


Fig. 2. Ligands used for optimization.

are often problematic coupling partners in palladium-catalyzed reactions. Accordingly, 4-methoxy phenyl 1,1,2,2,3,3,4,4-nonafluorobutane-1-sulfonate was first examined as the model substrate. Speculating the high reactivity of the electrophile, we explored a completely phosphine-free strategy on our model substrate. Unfortunately, a product could not form under this condition. Palladium catalysts along with bidentate ligands were found to provide true catalytic species, which was found to be the driving factor for the aminocarbonylation of triflates (Table 1). Therefore, a diverse set of bidentate ligands (Fig. 2) were screened in our model reaction. Among the bidentate ligands examined, the combination of palladium(II) acetate ($Pd(OAc)_2$) and xantphos was found to give superior results (Table 1, entry 8).

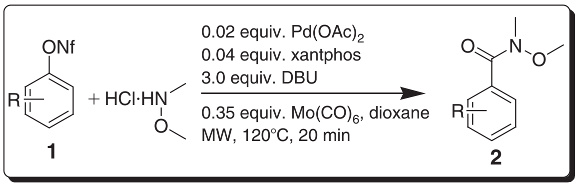
The optimized condition (Table 1, entry 8) was subsequently applied to a wide range of aryl/heteroaryl nonaflates bearing electron-donating or electron-withdrawing groups. All substrates studied produced exceptional results. The results are depicted as shown in Table 2, Notably, 4-nitro and 4-cyano nonaflates (activated systems) reacted much faster without any deleterious side reactions[51] (Table 2, entries 3 and 20). A great deal of generality was observed with nonaflates. Even sterically crowded aryl nonaflates were found to give excellent results under this reaction condition. (Table 2, entries 18 and 26).

The importance of hetero aromatic systems in the field of material science and medicinal chemistry prompted us to further expand the scope of this protocol on heterocyclic systems. This methodology was found to give good results, and reasonable yields of the amino-carbonylated products were obtained (Table 2, entries 7, 10, 13, and 28).

Chemoselective studies were also performed to check the reactivity of aryl nonaflates with halides (Table 3, entries 1 and 2). A mixture of products were obtained using 4-iodo and 4-bromo nonaflates, as anticipated. However, the 4-chloro nonaflate was found to be intact under the conditions explored (Table 3, entry 3).

Encouraged by these exciting results, we then explored this optimized reaction condition with respect to other amines. Excellent yields of the amino-carbonylated products were obtained (Table 4).

Table 2. Conversion of aryl/heteroaryl nonaflates to weinreb amide via Pd-catalyzed aminocarbonylation[A]



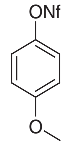
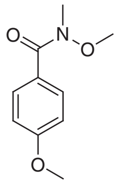
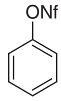
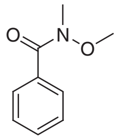
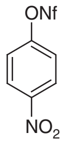
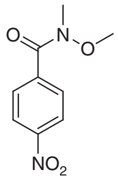
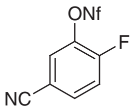
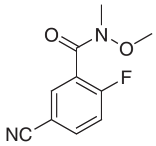
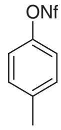
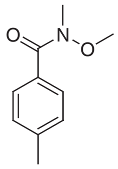
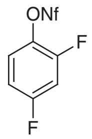
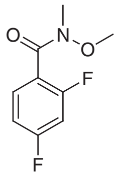
Entry	Ar-ONf	Product	Yield[B] [%]
1		 **2a**	87
2		 **2b**	91
3		 **2c**	92
4		 **2d**	90
5		 **2e**	90
6		 **2f**	79

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Table 2. (Continued)

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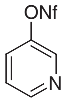
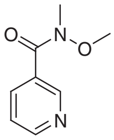
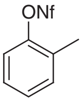
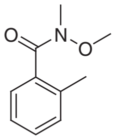
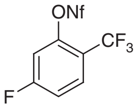
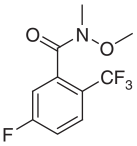
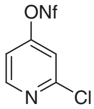
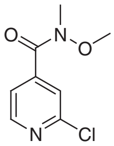
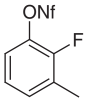
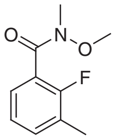
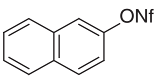
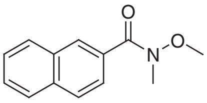
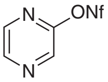
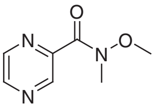
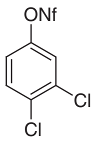
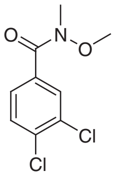
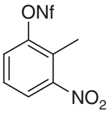
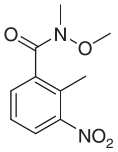
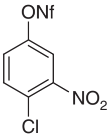
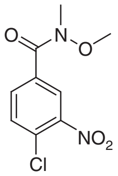
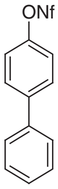
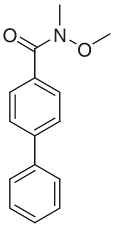
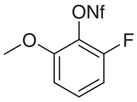
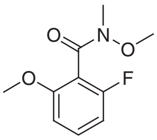
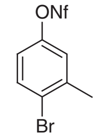
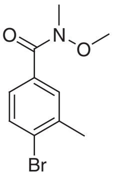
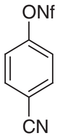
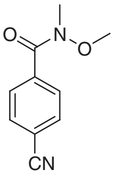
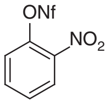
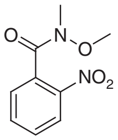
7		 **2g**	83
8		 **2h**	87
9		 **2i**	89
10		 **2j**	71
11		 **2k**	89
12		 **2l**	93
13		 **2m**	65
14		 **2n**	89
15		 **2o**	87
16		 **2p**	88
17		 **2q**	91
18		 **2r**	79
19		 **2s**	26^{C,D}
20		 **2t**	90
21		 **2u**	79

(*Continued*)

Table 2. (Continued)

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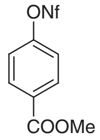
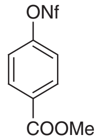
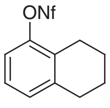
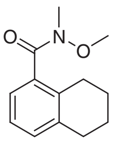
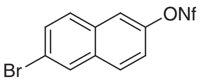
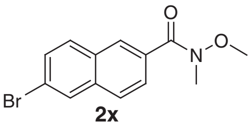
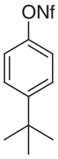
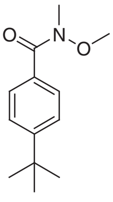
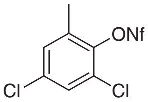
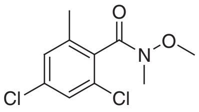
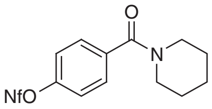
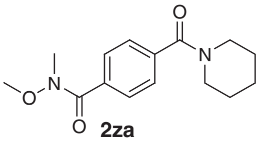
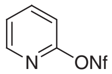
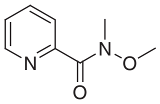
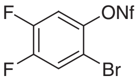
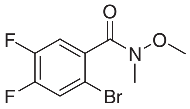
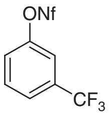
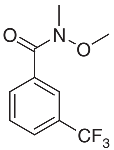
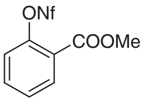
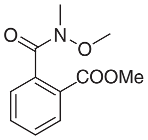
22		 **2v**	83
23		 **2w**	88
24		 **2x**	27^{C,D}
25		 **2y**	85
26		 **2z**	77
27		 **2za**	84
28		 **2zb**	67
29		 **2zc**	26^{C,D}
30		 **2zd**	86
31		 **2ze**	80

(*Continued*)

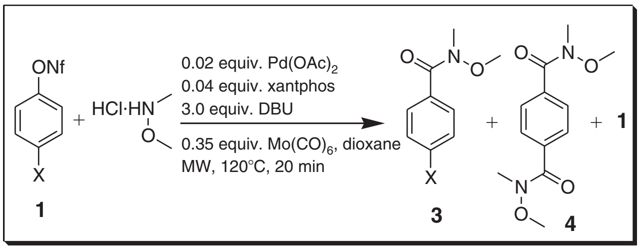
^{A}Reaction conditions: Pd(OAc)$_2$ (0.02 equiv.), xantphos (0.04 equiv.), aryl nonaflate (250 mg, 1.0 equiv.), amine (1.0 equiv.), Mo(CO)$_6$ (0.35 equiv.), DBU (3.0 equiv.) in dioxane (2 mL) at 120°C, 20 min, MW

^{B}Isolated yields.

^{C}A mixture of products were observed.

^{D}Conversion evaluated by gas chromatography–mass spectrometry (GC-MS).

Table 3. Chemoselective studies of aryl nonaflates^{A}



Entry	X	3^{B} [%]	4^{B} [%]	Recovery of **1**^{B}
1	4-Iodo **(1l)**	28	24	16
2	4-Bromo **(1k)**	26	30	13
3	4-Chloro **(1j)**	90	Traces	7

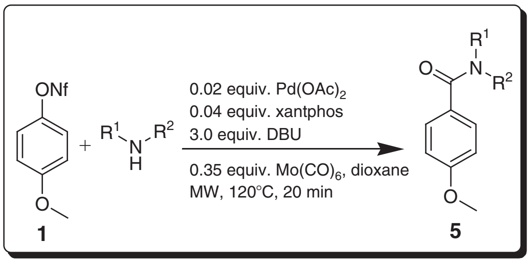
^{A}Reaction conditions: Pd(OAc)$_2$ (0.02 equiv.), xantphos (0.04 equiv.), aryl nonaflate (250 mg, 1.0 equiv.), amine (1.0 equiv.), Mo(CO)$_6$ (0.35 equiv.), DBU (3.0 equiv.) in dioxane (2 mL), 120°C, 20 min, MW

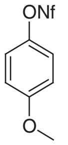
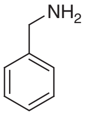
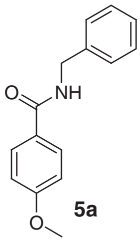
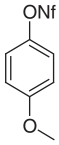
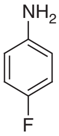
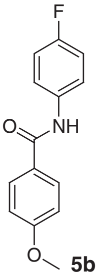
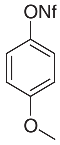
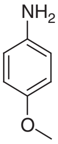
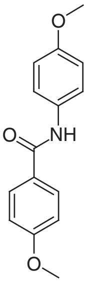
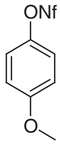
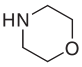
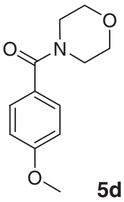
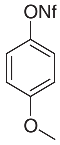
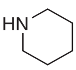
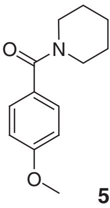
^{B}Conversion evaluated by GC-MS.

After demonstrating the synthetic utility of Mo(CO)$_6$-mediated palladium-catalyzed aminocarbonylation reaction of aryl/heteroaryl nonaflates, we studied the reactivity of other pseudo halides (OTs, OMs, OTf) and halides (I, Br, Cl) under similar conditions. The results are summarized in Table 5.

In Scheme 1, the general reaction mechanism for the sequential activation and palladium-catalyzed aminocarbonylation of phenyl nonaflate is shown. Phenyl nonaflate undergoes oxidative addition to the active Pd^0 phosphine species to form the corresponding arylpalladium(II) complex. After coordination and insertion of CO followed by the nucleophile attack of methoxy methyl amine, the phenyl weinreb amide is formed. Finally, under the assistance of base, the active Pd^0 species is regenerated.

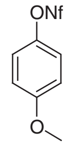
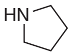
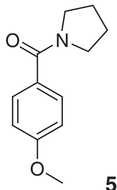
Table 4. Aminocarbonylation of aryl nonaflates using primary and secondary amines[A]



Entry	Ar-ONf	Amine	Product	Yield[B] [%]
1			 **5a**	91
2			 **5b**	92
3			 **5c**	90
4			 **5d**	91
5			 **5e**	89

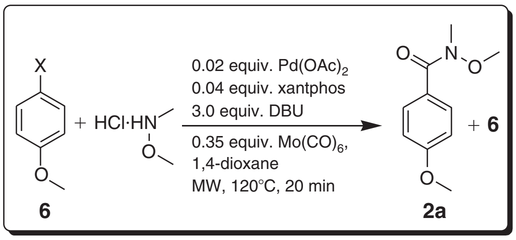
(*Continued*)

Table 4. (Continued)

Entry	Ar-ONf	Amine	Product	Yield^B [%]
6			 **5f**	90

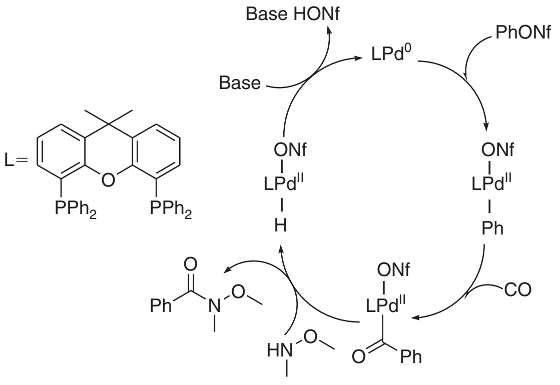
^{A}Reaction conditions: $Pd(OAc)_2$ (0.02 equiv.), xantphos (0.04 equiv.), aryl nonaflate (250 mg, 1.0 equiv.), amine (1.0 equiv.), $Mo(CO)_6$ (0.35 equiv.), DBU (3.0 equiv.) in dioxane (2 mL), 120°C, 20 min, MW
^{B}Isolated yields.

Table 5. Screening of different leaving groups under the optimized conditions^A



Entry	X	**2a**^{B} [%]	Yield^C [%]
1	OTs **(6a)**	50	35
2	OMs **(6b)**	6	Traces
3	OTf **(6c)**	64	44
4	4-Iodo	90	83
5	4-Bromo	85	79
6	4-Chloro	5	Traces

^{A}Reaction conditions: $Pd(OAc)_2$ (0.02 equiv.), xantphos (0.04 equiv.), aryl pseudo halide (250 mg, 1 equiv.), amine (1.0 equiv.), $Mo(CO)_6$ (0.35 equiv.), DBU (3.0 equiv.) in dioxane (2 mL), 120°C, 20 min, MW
^{B}Conversion evaluated by GC-MS.
^{C}Isolated yields.



Scheme 1. Proposed reaction mechanism.

Conclusion

A mild and efficient synthetic protocol for the aminocarbonylation of aryl/heteroaryl nonaflates using $Mo(CO)_6$ as a solid CO source under microwave-enhanced condition was developed (Tables 2, 4). The methodology was found to be tolerant to a wide range of functional groups. Comparative studies with respect to other pseudo halides revealed the superior reactivity and stability of nonaflates in aminocarbonylation reaction.

Supplementary Material

Experimental details, characterization and spectral data are available on the Journal's website.

Acknowledgements

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