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COMMUNICATION

Ruthenium(IV) porphyrin catalyzed phosphoramidation of aldehydes with phosphoryl azides as a nitrene source†‡

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[Ru^{IV}(por)Cl_2] (por = porphyrin dianion) can efficiently catalyze nitrene insertion into aldehyde C–H bonds with phosphoryl azides as a nitrene source to give *N*-acylphosphoramidates in good to high yields.

N-acylphosphoramidate is present in a number of bioactive natural and unnatural compounds such as Agrocin 84,[1] Microcin C7[2] and Phosmidosine[3] (Fig. 1) known to exhibit antifungal and antitumor activities. The synthetic procedures of phosphoramidate compounds mainly rely on phosphorylation of amides with chlorophosphonate,[4] acylation of phosphoramides with acyl chloride or mixed anhydrides,[5] and coupling of phosphoramidites with amides followed by oxidation.[6] However, the need to use a strong base such as butyllithium, limited substrate scope, and the requirement of multiple-step manipulation are the limitations of these literature methods. Therefore, it is desirable to develop a simple and efficient means for the construction of *N*-acylphosphoramidate.

A straightforward route to *N*-acylsulfonamides *via* transition metal-catalyzed nitrene insertion into aldehyde C–H bonds has recently been reported. Dirhodium(II) carboxylates,[7] ruthenium(II) porphyrins,[8] CuI/pyridine[9] and $FeCl_2$/pyridine[10] or terpyridine[11] have been proven to be effective catalysts for this transformation with PhI=NTs or $TsNH_2$/PhI(OC(O)^{t}Bu)$_2$ as a nitrene source. Organic azides as an alternative nitrene source have attracted considerable interest due to their versatility, easy accessibility and the formation of environmentally benign nitrogen gas as the only by-product in the catalysis. We and other groups have demonstrated that the porphyrin complexes of ruthenium(II),[12] iron(III)[13] and cobalt(II),[14] dirhodium(II) carboxylates,[15] and ruthenium(II) Schiff base complexes[16] can efficiently mediate nitrene insertion into sp^3 and sp^2 C–H bonds with organic azides. In previous work, we found that dichlororuthenium(IV) porphyrin [Ru^{IV}(por)Cl_2] displays substantially higher catalytic activity than its carbonyl analogue [Ru^{II}(por)(CO)] towards C–H bond oxidation, epoxidation of alkenes and E–I reaction of alkenes.[17] This result prompted us to examine the activity of [Ru^{IV}(por)Cl_2] towards nitrene transfer and insertion reactions with organic azides as a nitrene source, which is unprecedented in the literature. Herein, we describe a highly efficient Ru(IV) porphyrin-catalyzed phosphoramidation of aldehydes with phosphoryl azides to form *N*-acylphosphoramidates in good to high yields.

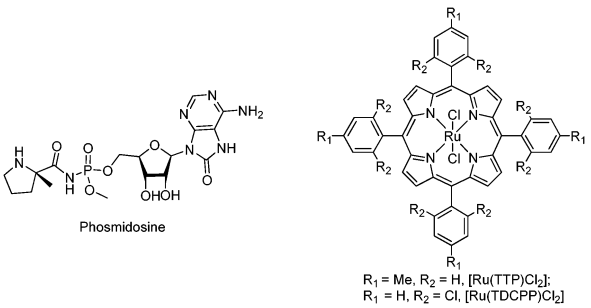

Fig. 1 Phosmidosine and dichlororuthenium(IV) porphyrins.

In our preliminary study, we examined the phosphoramidation of *p*-tolualdehyde by using diphenylphosphoryl azide (DPPA) as a nitrene source and [Ru^{II}(TTP)(CO)] [TTP = *meso*-tetrakis-(4-tolyl)porphyrin] as catalyst. Treatment of *p*-tolualdehyde with DPPA (1.5 equiv.) in the presence of catalytic amount of [Ru^{II}(TTP)CO] (5 mol%) in 1,2-dichloroethane under reflux for 12 h afforded *N*-acylphosphoramidate **2a** in 78% yield with 100% substrate conversion (Table 1, entry 1). In contrast, [Ru^{II}(F_{20}-TPP)(CO)], [Ru^{II}(*p*-cymene)Cl_2]$_2$, [CpRu^{II}(COD)Cl], [$Ru^{III}Cl_3 \cdot 3H_2O$], [Co^{II}(F_{20}-TPP)], [Fe^{III}(F_{20}-TPP)Cl], [$Rh^{II}_2(O_2CCF_3)_4$], and [$Cu^{II}(OTf)_2$] all failed to catalyse/mediate the phosphoramidation (entries 2–9) under similar reaction conditions. We then examined the phosphoramidation with [Ru^{IV}(TTP)Cl_2] as catalyst. Under similar reaction conditions, [Ru^{IV}(TTP)Cl_2] catalyzed the amidation to give **2a** in 92% yield and with 100% substrate conversion. With [Ru^{IV}(TDCPP)Cl_2] bearing a more bulky porphyrin ligand, a lower product yield was obtained (70%). The effects of temperature and solvent were examined. The reaction in dichloromethane at 40 °C gave the best result (entry 13, 99% yield and 100% substrate conversion). No reaction was observed in the absence of the ruthenium catalyst and with [Ru^{II}(TTP)(CO)] as catalyst at 40 °C.

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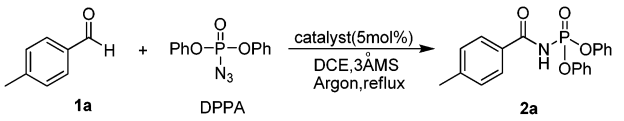
‡ Electronic supplementary information (ESI) available: Experimental procedures and compound characterization. See DOI: 10.1039/c2cc31686b

Table 1 Screening catalysts and conditions for phosphoramidation of aldehydes with phosphoryl azides[a]



1a DPPA 2a

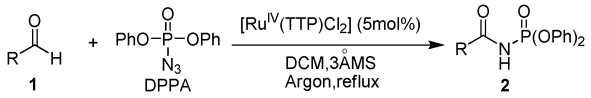
Entry	Catalyst	Solvent	Temp./ °C	Conv.[b] (%)	Yield[c] (%)
1	$[Ru^{II}(TTP)(CO)]$	DCE	84	100	78
2	$[Ru^{II}(F_{20}\text{-TPP})(CO)]$	DCE	84	NR[e]	
3	$[Ru^{II}(p\text{-cymene})Cl_2]_2$	DCE	84	NR	
4	$[CpRu^{II}(COD)Cl]$	DCE	84	NR	
5	$[Ru^{III}Cl_3{\cdot}3H_2O]$	DCE	84	NR	
6	$[Co^{II}(F_{20}\text{-TPP})]$	DCE	84	NR	
7	$[Fe^{III}(F_{20}\text{-TPP})Cl]$	DCE	84	NR	
8	$[Rh_2^{II}(O_2CCF_3)_4]$	DCE	84	NR	
9	$[Cu^{II}(OTf)_2]$	DCE	84	NR	
10[f]	$[Ru^{IV}(TTP)Cl_2]$	DCE	84	100	92
11[f]	$[Ru^{IV}(TDCPP)Cl_2]$	DCE	84	100	70
12	$[Ru^{IV}(TTP)Cl_2]$	DCE	40	100	85
13	$[Ru^{IV}(TTP)Cl_2]$	DCM	40	100	99
14	$[Ru^{IV}(TTP)Cl_2]$	Toluene	40	90	90
15[d]	$[Ru^{IV}(TTP)Cl_2]$	DCM	40	100	99
16	No catalyst	DCE	84	NR	

[a] *p*-Tolualdehyde (0.2 mmol), DPPA (0.3 mmol), 3 Å MS (25 mg), catalyst (5 mol%), solvent (1 mL), 12 h. [b] Conversion was determined based on aldehyde by using ^{1}H NMR. [c] Based on conversion. [d] DPPA (0.24 mmol, 1.2 equiv.). [e] NR = no reaction. [f] Reaction time = 3 h.

With the optimized conditions, we examined the substrate scope of $[Ru^{IV}(TTP)Cl_2]$-catalyzed amidation of aldehydes with DPPA. As depicted in Table 2, a variety of aryl and aliphatic aldehydes reacted with DPPA in the presence of $[Ru^{IV}(TTP)Cl_2]$ to give corresponding *N*-acylphosphoramidates in good to excellent yields (56–99%) with high substrate conversions (78–100%). This reaction shows excellent functional group tolerability as various functionalities including hydroxyl, nitro, halide, C=C groups and heterocycles are compatible with the protocol (entries 1–14). In line with the amidation of aldehydes with PhI=NTs catalyzed by CuI/pyridine[9] and $FeCl_2$/terpyridine,[10] electron-rich aryl aldehydes were more reactive than the electron-deficient ones using the "$[Ru^{IV}(TTP)Cl_2]$ + DPPA" protocol giving higher product yields and substrate conversions (entries 1–6). The electron-deficient 4-nitrobenzaldehyde, which was reported to be unreactive in the Cu(I) and Fe(II)-catalyzed amidation with PhI=NTs, could undergo aldehydic C–H bond insertion with DPPA to afford the corresponding product in 96% yield based on 70% substrate conversion (entry 6). When compared with aryl aldehydes, aliphatic aldehydes gave lower product yields of 60–62% (entries 12–13). In the case of amidation of 3-phenylpropanal where benzylic C–H bond amination is a potential competitive reaction, only the aldehyde phosphoramidation product was obtained in 62% yield (entry 13). Antipyrine is analgesic and antipyretic and is often used in testing the effects of other drugs or diseases of drug-metabolizing enzymes in the liver. When 4-antipyrine carboxaldehyde **1o** was used as a substrate, the phosphoramidation product was obtained in 56% yield and with 86% substrate conversion, the antipyrine moiety remained intact (entry 14).

We next investigated the scope of phosphoryl azides for the $[Ru^{IV}(TTP)Cl_2]$-catalyzed *p*-tolualdehyde amidation. As depicted

Table 2 $[Ru^{IV}(TTP)Cl_2]$-catalyzed phosphoramidation of aldehydes with DPPA[a]

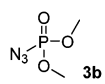
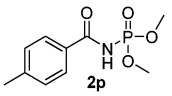
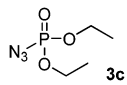
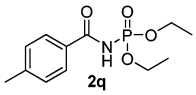
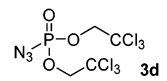
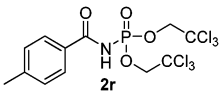
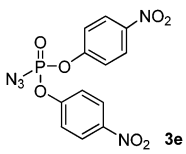
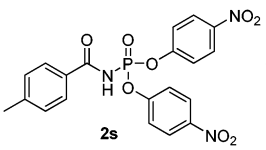


1 DPPA 2

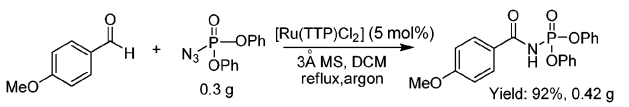
Entry	Aldehyde	Product	Conv.[b] (%)	Yield[c] (%)
1	1b	2b	100	85
2	1c	2c	100	95
3	1d	2d	100	98
4	1e	2e	95	99
5	1f	2f	100	74
6	1g	2g	70	96
7	1h	2h	100	85
8	1i	2i	78	78
9	1j	2j	100	79
10	1k	2k	100	71
11	1l	2l	100	89
12	1m	2m	100	62
13	1n	2n	100	60
14	1o	2o	86	56

[a] Aldehyde (0.2 mmol), DPPA (0.24 mmol), 3 Å MS (25 mg), $[Ru^{IV}(TTP)Cl_2]$ (5 mol%), CH_2Cl_2 (1 mL), 12 h. [b] Conversion was determined based on aldehyde by using ^{1}H NMR. [c] Based on conversion.

Table 3 [$Ru^{IV}(TTP)Cl_2$]-catalyzed phosphoramidation of *p*-tolualdehyde with phosphoryl azides[a]

Entry	Azide	Product	Conv.[b] (%)	Yield[c] (%)
1	 3b	 2p	100	99
2	 3c	 2q	100	85
3	 3d	 2r	100	99
4	 3e	 2s	100	99

[a] *p*-Tolualdehyde (0.2 mmol), DPPA (0.24 mmol), 3 Å MS (25 mg), [Ru(TTP)Cl_2] (5 mol%), CH_2Cl_2 (1 mL), 12 h. [b] Conversion was determined based on aldehyde by using ^1H NMR. [c] Based on conversion.



Scheme 1

in Table 3, various substituents of phosphoryl azide including methyl, ethyl, 2,2,2-trichloroethyl, and *p*-nitrophenyl groups are compatible with the protocol, and all of them led to excellent product yields (85–99%) and 100% substrate conversion.

The Ru(IV)-catalyzed synthesis of *N*-acylphosphoramidate can be scaled up. Slow addition of a solution of DPPA (0.33 g) in DCM (2 mL) to a mixture of [$Ru^{IV}(TTP)Cl_2$] (5 mol%) and 4-methoxybenzaldehyde (0.14 g) in DCM (3 mL) for 5 h at 40 °C afforded the amidation product in 92% yield (0.42 g, Scheme 1).

The deuterium kinetic isotope effect for the reaction of benzaldehyde, benzaldehyde-d_6 and $N_3P(O)(OCH_2CCl_3)_2$ gave a k_H/k_D value of 4.1, revealing rate determining carbon–hydrogen bond cleavage. The catalysis probably involves the formation of a reactive (imidophosphoryl)ruthenium species. A possibility is that bis(imidophosphoryl)ruthenium(VI) porphyrin[18] is formed initially by the reaction of dichlororuthenium(IV) porphyrin with phosphoryl azide, which is analogous to the oxidation of dichlororuthenium(IV) porphyrin to dioxoruthenium(VI) porphyrin by O_2.[17d] This putative intermediate undergoes nitrene insertion into the aldehyde C–H bond to give *N*-acylphosphoramidate. The high activity of dichlororuthenium(IV) porphyrin probably stems from Ru(IV) which facilitates the decomposition of phosphoryl azide to generate the ruthenium–imido/nitrene species and subsequent nitrene insertion into the aldehydic C–H bond.

In conclusion, we have developed an efficient method for the synthesis of *N*-acylphosphoramidates with excellent chemoselectivity and functional group tolerability *via* nitrene insertion into aldehyde C–H bonds with phosphoryl azides as a nitrene source.

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