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[A006]

BENZYLIC NEWMAN-KWART REARRANGEMENT TRIGGERED BY PHOSPHANES

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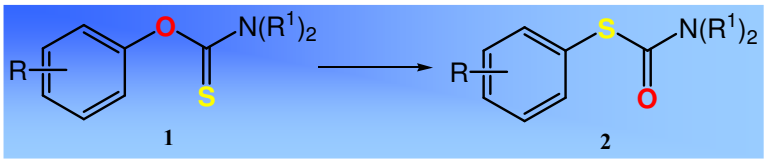
Abstract: A Staudinger imination reaction of tertiary phosphanes with *O*-(azidobenzyl)thioncarbamates, bearing the azido function at *ortho* or *para* position, promotes a rare benzylic Newman-Kwart rearrangement.

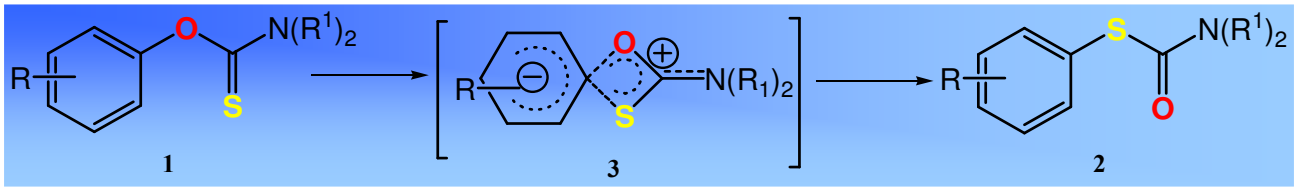
1. Introduction

Reported for the first time in 1966,[1] the Newman-Kwart rearrangement (NKR) is a first-order unimolecular rearrangement converting *O*-aryl thioncarbamates **1** into their *S*-aryl isomers **2** under heating at temperatures between 150 and 350 ºC **(**Scheme 1**).**



Scheme 1. NKR in aryl compounds

The activating role of the electron-withdrawing substituents at the aromatic nucleus is the basis on which the commonly acepted mechanism for the NKR rests: an intramolecular aromatic nucleophilic substitution reaction that, unlike the classic intermolecular SNAr, has been characterized by experimental and computational studies, as a concerted process [2] (Scheme 2).



Scheme 2. Mechanism of the Newman-Kwart rearrangement

The applications of this rearrangement are very diverse, as for example the synthesis of aromatic and heteroaromatic thiols [3], stilbenethiols [4],(see the examples shown in Figure 1), or the preparation of products of great usefulness in the dye industry as the spiroindolinobenzothiopyrans **I** [5] (Figure 1).

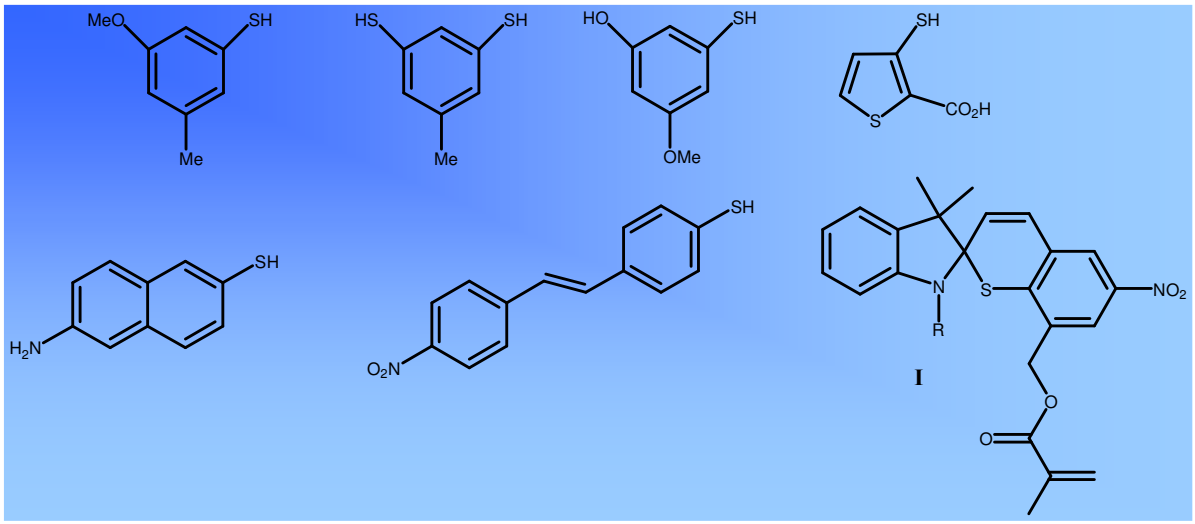
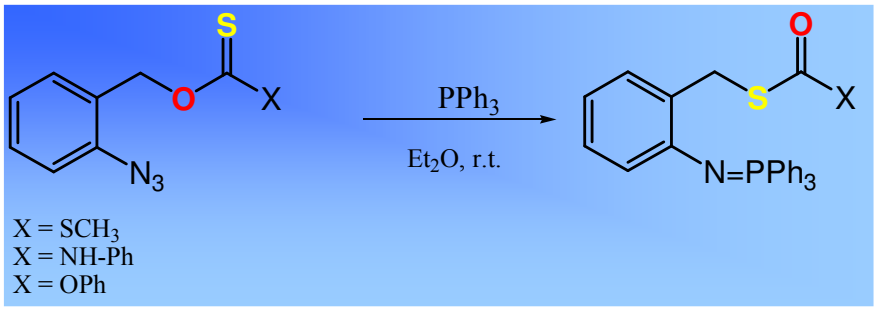


Figure 1. Compounds prepared by NKR

Within the frame of our recent investigations on radical reactions of ketenimines [6] we discovered an unexpected 1,3 rearrangement of an *o*-functionalized benzylic fragment. When several *O*-benzyl thionoderivatives bearing an azide function at *ortho* position of the aromatic nucleus were submitted to the Staudinger imination reaction [7] with triphenylphosphine, the reaction products resulted to be the respective iminophosphoranes in which the benzylic fragment moved from O to S (Scheme 3).

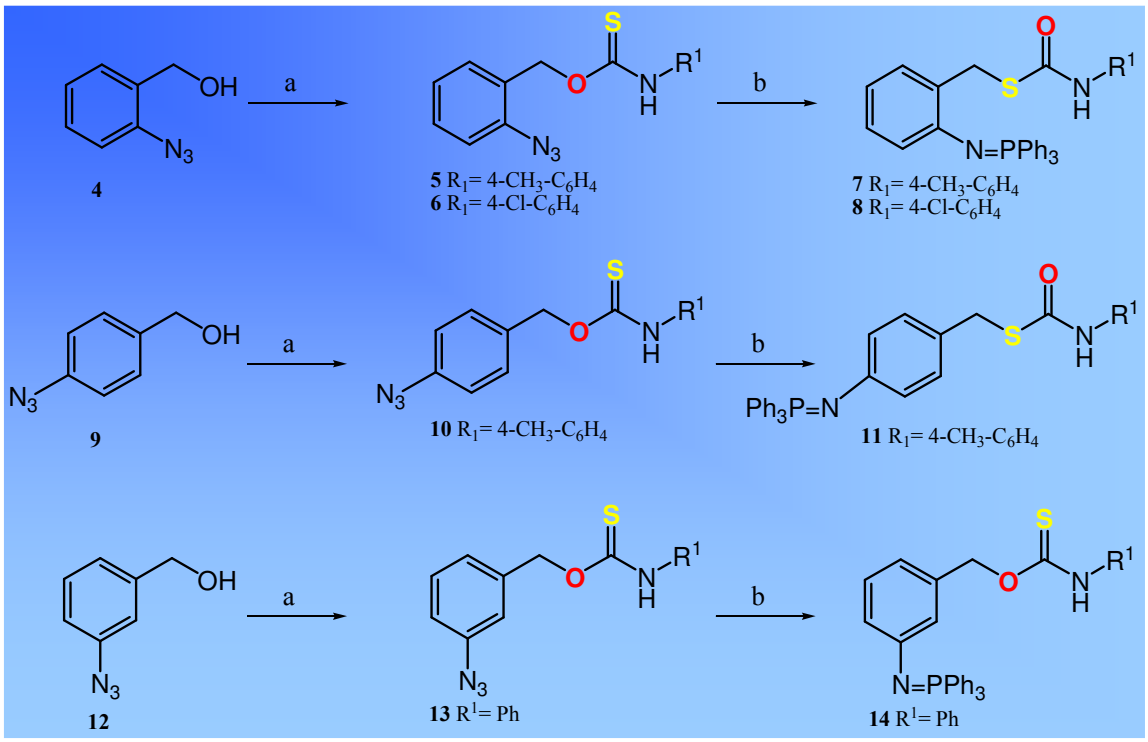


Scheme 3. 1,3 benzylic *O* to *S* rearrangement

These results captured our attention and we decided to go further in the study of this type of reactions by changing the position of the azido group in the aromatic ring, from *ortho* to *meta* and *para*.

2. Results and Discusion

The treatment of azidobenzyl alcohols **4**, **9** and **12** with sodium hydride and arylisothiocyanates, in tetrahydrofuran solution at room temperature, provided the *N*-aryl-*O*-(azidobenzyl)thioncarbamates **5-6**, **10** and **13**, respectively. The Staudinger reaction of these azides with triphenylphosphine, in diethyl eter solution at room temperature, afforded the iminophosphoranes **7-8**, **11** and **14**. It is noteworthy that only in compounds **7-8** and **11** the benzyl fragment has experienced an *O*- to *S*- transposition. This result is clearly indicative of the fact that the electron-releasing iminophosphorane substituent should be at *ortho* or *para* position with respect to the benzylic carbon for promoting the 1,3-benzylic *O*- to *S*- transposition (Scheme 5). It is worth pointing out that, in our hands, thioncarbamates derived from benzyl alcohol remained unaltered when toluene solutions were heated at reflux temperature for 48 h.



Scheme 4. *Reagents and conditions*: (a) R^1-N=C=S, NaH, tetrahydrofuran, r.t., 16 h; (b) PPh_3, diethyl eter, r.t., 3-6 h

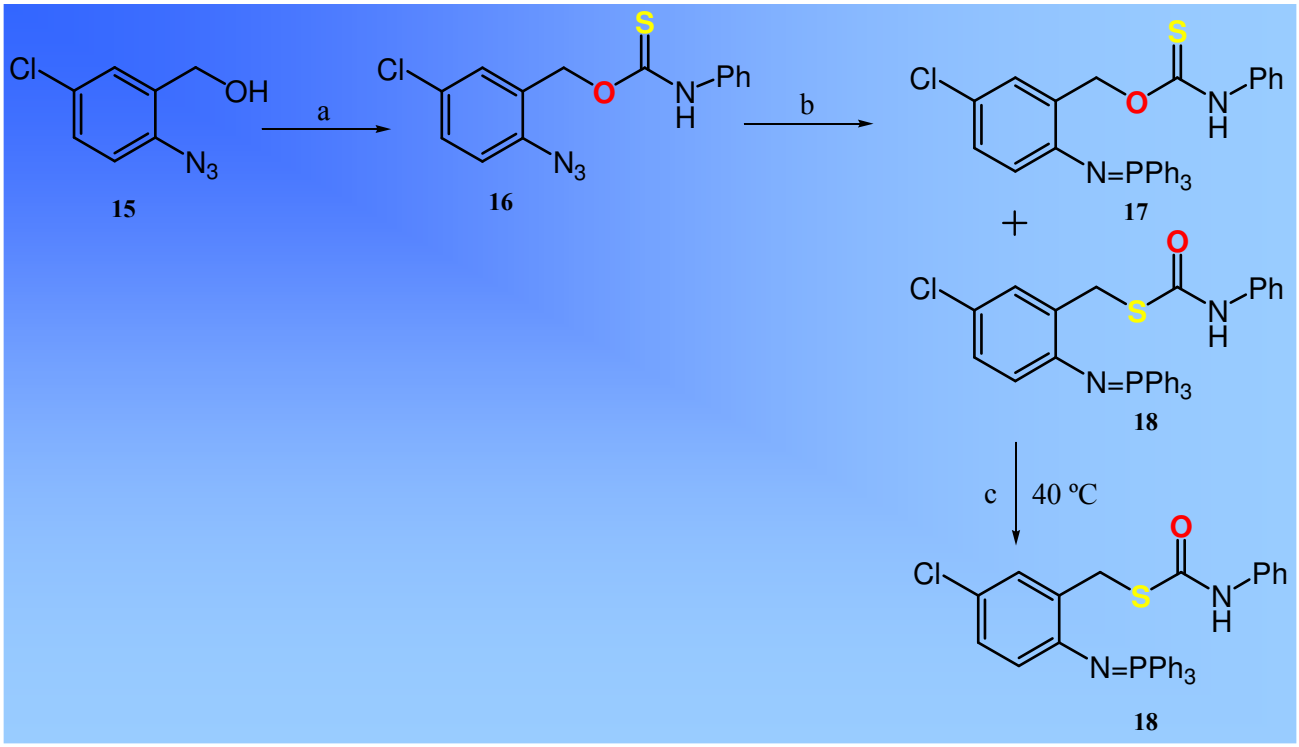
The determination of the structure of the rearranged *S*-benzyl thiocarbamates was essentially based on their ^1H and ^{13}C NMR spectroscopic data. Of particular relevance were the chemical shifts of the protons of the benzylic methylene group in their ^1H NMR spectra, and the chemical shifts of the carbon atom of that group in their ^{13}C NMR spectra. In all cases, a notable upfield shift was observed for the above mentioned nuclei when compared with their chemical shifts in the predecessor *O*-benzyl thioncarbamates (Table 1).

Table 1. Selected NMR data

Compound	δ_H CH_2[a]	δ_C CH_2[a]	Compound	δ_H CH_2[b]	δ_C CH_2[b]
5	5.48	66.3	**7**	4.54	32.8
6	5.48	66.8	**8**	4.51	32.9
10	5.55	70.3	**11**	4.10	34.6
16	5.57	69.9	**17**	5.31	73.9

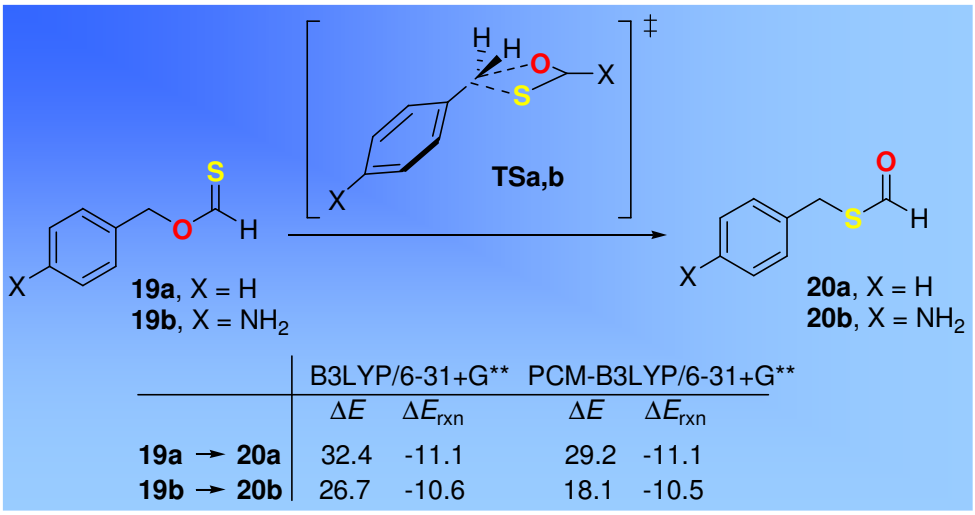
[a] Spectral data in DMSO
[b] Spectral data in $CDCl_3$

The Staudinger imination reaction of *N*-phenyl-*O*-(2-azido-5-chlorobenzyl) thioncarbamate **16** with triphenylphosphine, at room temperature, resulted in a mixture of the *S*-benzyl rearranged iminophosphorane **18**, and its structural isomer non-rearranged *O*-benzyl iminophosphorane **17**. Subsequent heating of the mixture (**17** and **18)** at 40 ºC**,** without any solvent, drove to the completion of the conversion **17→18** (Scheme 6).Thus, the presence of an electron-withdrawing chlorine atom in the benzene ring of the benzyl component in *para* position to the iminophosphorane group makes more difficult the 1,3-benzylic oxygen to sulfur migration.



Scheme 5. *Reagents and conditions*: (a) Ph-NCS, NaH, tetrahydrofuran, r.t.,16 h; (b) PPh_3, diethyl eter, r.t., 3 h; (c) 24 h

The mechanism for the transformation of the structurally simpler models *O*-benzylthioesters **19a,b** into the corresponding *S*-benzylthiolesters **20a,b** (Scheme 7) has been approached by using density functional theory at the Becke3LYP/6-31+G** and the PCM-B3LYP/6-31+G** (using diethylether as solvent) levels. The computational study reveals that these transformations involve a concerted [1,3]-shift of the benzyl group through the transition states **TSa,b**. The energy barrier for the [1,3] benzyl shift in **19b** has been computed to be lower (26.7 kcal/mol at the Becke3LYP/6-31+G**) than that corresponding to the conversion **19a→20a** (32.4 kcal/mol), both processes being exothermic (by 10.6 and 11.1 kcal/mol respectively). The inclusion of diethylether as solvent lowers significantly the barrier computed for the conversion **19b→20b** (18.1 kcal/mol).



	B3LYP/6-31+G**		PCM-B3LYP/6-31+G**	
	ΔE	ΔE_{rxn}	ΔE	ΔE_{rxn}
19a → 20a	32.4	-11.1	29.2	-11.1
19b → 20b	26.7	-10.6	18.1	-10.5

Scheme 6. Mechanism for the transformation *O*-benzylthioesters into the corresponding *S*-benzylthioesters

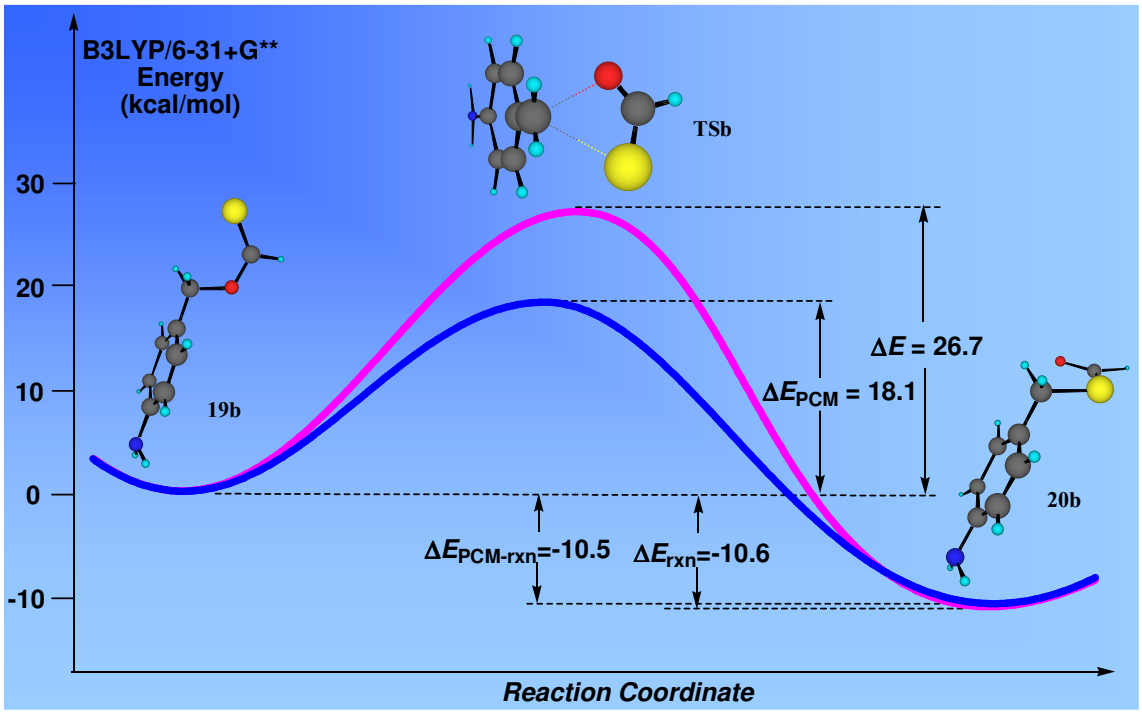


Figure 2. Qualitative reaction profiles at the B3LYP/6-31+G**/B3LYP-6-31+G** (in purple) and PCM-B3LYP/6-31+G**/PCM-B3LYP-6-31+G** (in blue, diethyl ether as solvent) of the [1,3] benzyl shift in *O*-benzylthioester **1b** leading to *S*-benzylester **2b** through the transition structure **TSb**

The transition states are notably zwitterionic, with a cationic benzylic part and an anionic thiocarboxylate fragment. This fact explains why the rearrangement is favoured by electron-releasing substituents at *o*- and *p*- position (the iminophosphoranyl groups used in the experimental work) contributing to stabilize the transition state, at its cationic part, via mesomeric effects.

3. Experimental

Preparation of *O*-benzyl thioncarbamates 5-6, 10, 13 and 16.
To a solution of the corresponding azidobenzyl alcohol **4**, **9**, **12** and **15** (5 mmol) and the aryl isothiocyanate in anhydrous tetrahydrofuran (25 mL) sodium hydride (60 % in oil; 0.25 g, 6.25 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen for 16 h. Then the tetrahydrofuran was removed under reduced pressure and the resulting material was partitioned between dichlorometane (30 mL) and water (30 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. After evaporation of the solvent the residue was chromatographed [silica gel, hexanes/diethyl ether (7:3) as eluent].

Representative analytical and spectroscopic data:

Compound 5: Yield 63%; mp: 104-106 ºC (colourless prisms); IR (Nujol) ν: 3212 (s), 3030 (m), 2126 (vs), 1592 (s) , 1541 (vs), 1489 (s), 1405 (s), 1359 (vs), 1308 (m), 1285 (s), 1181 (s), 1155 (vs), 1097 (m), 1019 (s), 823 (m), 751 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6, 60 ºC, 300 MHz) δ: 2.26 (s, 3H), 5.48 (s, 2H), 7.11 (d, 2H, J = 8.4 Hz), 7.20 (t, 1H, J = 7.3 Hz), 7.31-7.47 (m, 6H), 10.87 (s, 1H);^{13}C NMR (DMSO-d_6, 60 ºC, 75 MHz) δ: 19.6,

66.3, 118.1, 122.0, 124.3, 126.6 (s), 128.2, 129.2 , 129.5, 133.7(s), 135.2 (s), 137.5 (s), 187.0 (s); HRMS (EI) : m/z: calcd for $C_{15}H_{19}N_2OS$: 270.0827; found: 270.0828.

Preparation of triphenylphosphazenes 7-8, 11, 14, 17 and 18.
To a solution of the corresponding azide **5-6, 10, 13,** and **16** (5 mmol) in anhydrous diethyl ether (15 mL) triphenylphosphane (1.31 g, 5 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen for 3-6 h. Then, the precipitaded compounds were isolated by filtration.

Representative analytical and spectroscopic data:

Compound 7: Yield 66%; mp 118-121 ºC (colourless prisms); IR (Nujol) ν: 3266 (s), 1674 (s), 1624 (s), 1591 (s), 1517 (s), 1480 (vs), 1309 (s), 1239 (s), 1152 (s), 1108 (vs), 1049 (m), 1021 (m), 813 (m), 749(s), 715 (s), 694 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.28 (s, 3H), 4.54 (s, 2H), 6.45 (d, 1H, *J* = 7.6 Hz), 6.63 (t, 1H, *J* = 7.2 Hz), 6.81 (td, 1H, *J* = 7.6, 1.6 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.35-7.46 (m, 6H), 7.50-7.54 (m, 3H), 7.73-7.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.8, 32.8, 117.4, 120.2, 120.7 (d, *J* = 9.8 Hz), 127.8, 128.6 (d, *J*= 10.0 Hz),129.4, 129.9 (d, *J* = 2.0 Hz), 131.1 (d, *J* = 99.6 Hz) (s), 131.7 (d, *J* = 2.3 Hz), 132.0 (d, *J* = 11.9 Hz) (s), 132.5 (d, *J* = 9.7 Hz), 133.6 (s), 135.6 (s), 149.5 (s), 167.4 (s); ^{31}P NMR ($CDCl_3$, 121.4 MHz) δ: 2.76; HRMS (EI): m/z: calcd for $C_{32}H_{29}N_2OPS$: 532.1738; found: 532.1752.

Acknowledgements

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