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Phosphine-Catalyzed Difunctionalization of β-Fluoroalkyl α,β-Enones: A Direct Approach to β-Amino α-Diazo Carbonyl Compounds

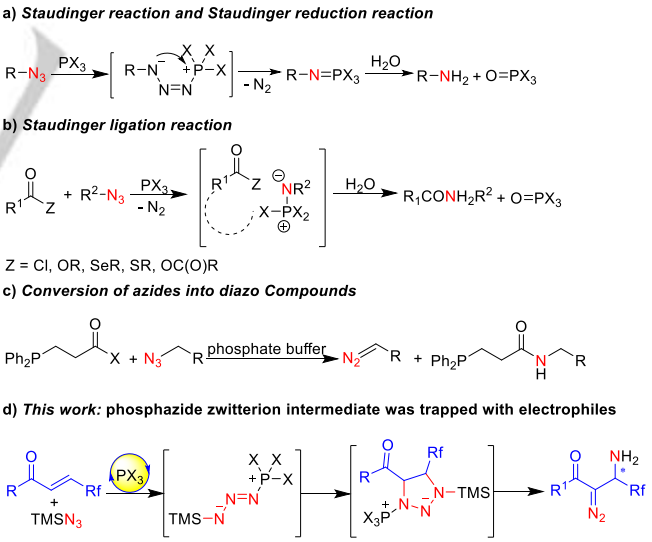
Huamin Wang,[a] Li Zhang,[b] Youshao Tu,[a] Ruiqi Xiang[a] Yin-Long Guo,*[b] and Junliang Zhang*[b,c]

Dedicated to Professor Xiyan Lu for his 90th birthday

Abstract: *An efficient and practical phosphine-catalyzed vicinal difunctionalization of β-fluoroalkyl α,β-enones with $TMSN_3$ has been developed. Using DPPB as the catalyst, the reaction worked efficiently to yield various β-amino α-diazocarbonyl compounds in high yields (up to 94%). This work marks the first efficient construction of α-diazocarbonyl compounds by phosphine catalysis. Meanwhile, the asymmetric variant induced by the nucleophilic bifunctional phosphine* ***P4*** *led to various chiral fluoroalkylated β-amino α-diazocarbonyl compounds in high yields and enantioselectivity. NMR and ESI-MS studies support the existence of the key reaction intermediates. In contrast, β-azide carbonyl compounds would be furnished in good yields from β-fluoroalkylated β,β-disubstituted enones.*

Azides, as a class of significant valuable building blocks, have been utilized to construct many usful frameworks.[1] In past decades, many methods has been developed for azide-involved transformations with classical phosphine-mediated[2] or -catalyzed reactions.[3] Among these methods, the Staudinger reaction has received much attention in the field of chemistry and chemical biology.[2a-d] This reaction proceeds through nucleophilic addition of the phosphine at the terminal nitrogen atom of the azide to form a phosphazide intermediate, the iminophosphorane was then formed after releasing a molecular of N_2.[2b,d] It's fameous name reactions were then developed by traping the iminophosphorane intermediate of Staudinger reaction. For example, Staudinger reduction reaction is the iminophosphorane intermediate reacting with water to produce the amide (Scheme **1a**). Besides the water, the phosphazide intermediate could be traped by carboxylic acid derivatives, leading to amide product, which is called Staudinger ligation (Scheme **1b**).[2e,f,] In 2013, a significant contribution was made by Raines,[4,5] demonstrating the efficient conversion of azides into diazo compounds in phosphate buffer at neutral pH at room temperature (Scheme **1c**). In this elegant work, the reaction proceeds through the decomposition of an acyl triazene rather than the release of a molecule of N_2. To the best of our knowledge, the introduction of three nitrogen atoms of azide into organic compounds via Staudinger phosphazide intermediate without requiring stoichiometric amount of phoshine or extra reductant has not been reported thus far, and if it works, which will further improve the atom-economy and enrich the azide chemistry.

During our continuous efforts in developing phosphine-catalyzed[6,7] diverse transformations[8], we envisaged that the phosphazide zwitterion intermediate might be competitively trapped with a electrophile, *i.e.* enones by slowing down the generation of the iminophosphorane, involving intramolecular nucleophilic addition to generate the key triazole intermediate, subsequent fragmentation of generated β-amino α-diazo carbonyl compounds. If this hypothesis succeeds, we may open a new window for transformations of azide into synthetic useful compounds with the use of phosphine catalyst. Herein we reported the first enantioselective phosphine-catalyzed difunctionalization of alkene by β-fluoroalkylated α,β-enone with $TMSN_3$, furnishing a facile access to fluoroalkylated β-amino α-diazo carbonyl compounds (Scheme **1d**). Further study has revealed that the fluorine effect plays a very important role in this transformation.



Scheme 1. Phosphine-involved azide conversion.

In order to slow down the N_2-releasing step from phosphazide zwitterion intermediate to the iminophosphorane , we selected $TMSN_3$ with a bulky TMS group as the azide. The reaction of $TMSN_3$ with β-perfluoroalkyl enone (*Z*)-**1a** or (*E*)-**1a** indeed worked smootly in toluene under argon atmosphere in the presence of 10 mol% of 1,4-bis(diphenylphosphino)butane (DPPB), delivering β-amino α-diazo carbonyl compound **2a** in 81% yield (Table 1, Entry 1 and 2). Aryl enones bearing electron-donating, halogen or electron-withdrawing substituent on phenyl ring were successfully converted to the corresponding diazo products in moderate to excellent yields (55-92%, **2b-2n**)

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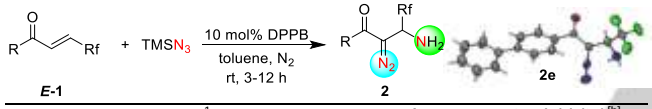
(Table 1, Entries 3-15). The structures of diazo compounds **2** were further confirmed by the X-ray single crystal analysis of **2e.**[9] Moreover, substrates bearing methanesulfonyl and methylthio group on the aryl ring were also smoothly converted to the desired diazo product **2o** (78%) and **2p** (69%), respectively (Table 1, Entry 16 and 17). The reactions of *ortho*- and *meta*-substituted aryl enones delivered **2q-2t** in good yields (Table 1, Entries 18-21). Multiply substituted aryl enones also worked well, affording **2u**-**2v** in moderate to good yields (48-70%) (Table 1, Entry 22 and 23). Moreover, naphthyl- and heteroaryl-substituted diazo compounds **2w-2aa** could be also obtained in 50-94% yields (Table 1, Entries 24-28). To our delight, aliphatic enones such as cyclohexyl (**1ba**) and cyclohexenyl (**1ca**) also proceeded smoothly to furnish the desired products, albeit with relatively lower efficiency (Table 1, Entry 29 and 30). Furthermore, the trifluoromethyl group could be replaced by other perfluoroalkyl group such as perfluoropropyl, perfluoroethyl and even difluoromethyl group, furnishing moderate to good yields of the desired diazo products **2da**, **2ea**, and **2fa** (Table 1, Entries 31-33). It is noteworthy that ethyl *4,4,4*-trifluorocrotonate was also applicable to give **2ga** in reasonable yield (Table 1, Entry 34). When the $TIPSN_3$ and $TESN_3$ instead of $TMSN_3$, the reaction still proceeded smoothly and gave the corresponding product **2g** in 57% and 71% yields, respectively (Table 1, Entries 35 and 36).

Table 1: Scope of the perfluoroalkylated α,β-enones.[a]



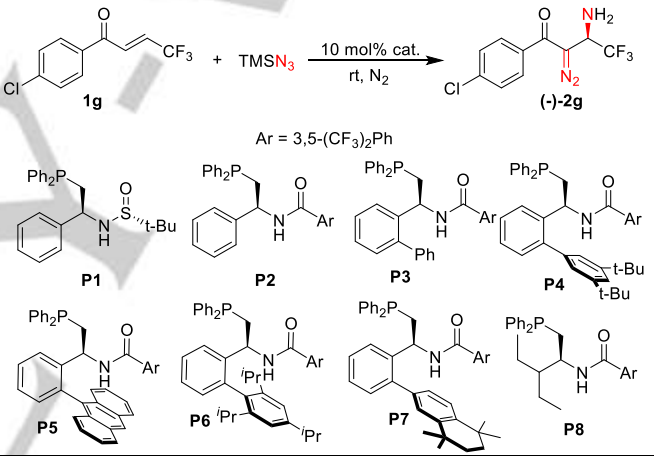
E-1 2

Entry	1, R^1	Rf	2, Yield (%)[b]
1	**E-1a**,Ph	CF_3	**2a,** 81
2	**Z-1a**	CF_3	**2a,** 79
3	**1b**, 4-MeC_6H_4	CF_3	**2b,** 80
4	**1c**, 4-isobutylphenyl	CF_3	**2c,** 79
5	**1d**, 4-$MeOC_6H_4$	CF_3	**2d,** 92
6	**1e**, 4-PhC_6H_4	CF_3	**2e,** 78
7	**1f**, 4-FC_6H_4	CF_3	**2f,** 73
8	**1g**, 4-ClC_6H_4	CF_3	**2g,** 73
9	**1h**, 4-BrC_6H_4	CF_3	**2h,** 75
10	**1i**, 4-IC_6H_4	CF_3	**2i,** 70
11	**1j**, 4-$F_3COC_6H_4$	CF_3	**2j,** 69
12	**1k**, 4-$F_3CC_6H_4$	CF_3	**2k,** 60
13	**1l**, 4-$NO_2C_6H_4$	CF_3	**2l,** 55
14	**1m**, 4-CNC_6H_4	CF_3	**2m,** 63
15	**1n**, 4-$MeO_2CC_6H_4$	CF_3	**2n,** 82
16[c]	**1o**, 4-$MeO_2SC_6H_4$	CF_3	**2o,** 78
17	**1p**, 4-$MeSC_6H_4$	CF_3	**2p,** 69
18	**1q**, 2-$NO_2C_6H_4$	CF_3	**2q,** 76
19	**1r**, 3-$NO_2C_6H_4$	CF_3	**2r,** 78
20	**1s**, 3-FC_6H_4	CF_3	**2s,** 70
21	**1t**, 3-BrC_6H_4	CF_3	**2t,** 75
22	**1u**, 3,4-$Cl_2C_6H_3$	CF_3	**2u,** 70
23	**1v**, 3,4-$(CF_3)_2C_6H_3$	CF_3	**2v,** 48
24	**1w**, 1-naphthyl	CF_3	**2w,** 73
25	**1x**, 2-naphthyl	CF_3	**2x,** 94
26	**1y**, 2-benzothienyl	CF_3	**2y,** 50
27	**1z**, 2-furyl	CF_3	**2z,** 72
28[d]	**1aa**, 2-pyridyl	CF_3	**2aa,** 63
29	**1ba**, cyclohexyl	CF_3	**2ba,** 50
30	**1ca**, 1-cyclohexenyl	CF_3	**2ca,** 43
31	**1da**, Ph	C_2F_5	**2da,** 84
32	**1ea**, Ph	C_3F_7	**2ea,** 87
33	**1fa**, Ph	CF_2H	**2fa,** 67
34	**1ga**, EtO	CF_3	**2ga,** 33
35[e]	**1g**	CF_3	**2g,** 57%
36[f]	**1g**	CF_3	**2g,** 71%

[a] Reactions were performed with **1** (0.2 mmol), $TMSN_3$ (0.4 mmol), and DPPB (0.02 mmol) in toluene (1.0 mL) at room temperature . [b] Yield of isolated product. [c] Carried out in 2 mL of toluene/DCM (V:V = 1:1). [d] Using Ph_2PCH_3 (10 mol%) as catalyst. [e] $TIPSN_3$ instead of $TMSN_3$. [f] $TESN_3$ instead of $TMSN_3$. $TMSN_3$ = azidotrimethylsilane. $TIPSN_3$ = azidotriisopropylsilane. $TESN_3$ = azidotriethylsilane. DCM = Dichloromethane.

After establishing a general and reliable method for the synthesis of unprecedented fluoroalkylated β-amino α-diazo carbonyl compounds, we next focused on the development of an enantioselective version mediated by a chiral phosphine. To our delight, using chiral sulfinamide phosphines **P1** as the catalyst, enone **1g** and $TMSN_3$ were reacted in toluene at room temperature, giving chiral β-amino α-diazo carbonyl compound **2g** in 40% yield and promising enantioselectivity (e.r. 55.5:44.5) (Table 2, entry 1). An array of other chiral phosphine amide catalysts were also examined, We were pleased to discover that using catalyst **P4**[8f], bearing a bulky 3,5-*di*-*tert*-butylphenyl substituent, product **(-)-2g** was obtained in 61% yield with *e.r.* of 89.5:10.5 (Table 2, entries 2-7). The dipeptide backbone catalyst gave inferior enantioselectivity and yield (Table 2, entry 8). Survey of the solvents revealed that *o*-xylene was the choice in terms of enantioselectivity (Table 2, entries 9-12). When increasing the catalyst loading from 10 to 20 mol%, gave a increase in yield (Table 2, entry 13). Lowering the reaction temperature to 0 °C inhibited the reaction (Table 2, entry 14).

Table 2: Asymmetric difunctionalization of β-perfluoroalkyl enone **1g** to $TMSN_3$ catalyzed by phosphines.[a]



Entry	Cat	Solvent	Yield [%][b]	*E.r.*[c]
1	**P1**	toluene	40	55.5:44.5
2	**P2**	toluene	55	74:26
3	**P3**	toluene	45	83:17
4	**P4**	toluene	61	89.5:10.5
5	**P5**	toluene	60	82.5:17.5
6	**P6**	toluene	55	76.5:23.5
7	**P7**	toluene	70	88.5:11.5
8	**P8**	toluene	50	76:24
9	**P4**	DCM	66	83.5:16.5
10	**P4**	$CHCl_3$	68	86.5:13.5
11	**P4**	THF	69	81:19
12	**P4**	*o*-xylene	60	91.5:8.5
13[d]	**P4**	*o*-xylene	77	91.5:8.5
14[d,e]	**P4**	*o*-xylene	trace	--

[a] Reaction conditions: **1g** (0.1 mmol), $TMSN_3$ (0.2 mmol), and the catalyst (0.01 mmol) in the solvent specified (1 mL) at room temperature for 10 h. [b] ^{19}F NMR yield with $PhCF_3$ as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **P4** was used 20 mol%. [e] At 0 °C. THF = Tetrahydrofuran. $CHCl_3$ = Chloroform.

With the optimal reaction conditions in hand, we were subsequently to explore the generality of this reaction with a variety of β-perfluoroalkyl enones, and the results are shown in Table 3. The substituents containing electron-withdrawing groups, and electron-donating groups on aromatic ring moiety of enones **1a−e** were well tolerated and resulted in good yields (69−91%) and with good enantioselectivities (Table 3, entries 1-14). The absolute configuration of the resulting in (-)-**2e** was

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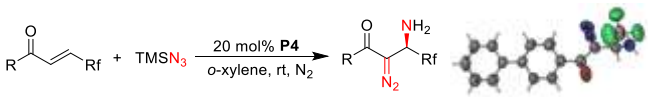
unambiguously determined to be (*R*) by an X-ray crystallographic analysis.[9] However, strong electron-withdrawing group on the aryl seemed to lead to slightly decresed *e.r.* (Table 3, entries 9-11). Moreover, benzen- and heteroaryl-fused enones are also suitable substrates, affording products **(-)-2w-2z** in good yields and stereoselectivity (Table 3, entries 15-18). In addition to trifluoromethyl enones, other fluoroalkyl enone, including pentafluoroethyl enone **1da**, heptafluoropropyl enone **1ea**, and difluoromethyl enone **1fa**, were examined, which also worked smoothly with the protocol (Table 3, entries 19-21). In addition, some other silicon azides were synthesized, and evaluated for reaction with **1a** under the optimized reaction conditions. $TBSN_3$ and $TESN_3$ are also well tolerated, affording **(-)-2a** with *e.r.* of 89:11 and *e.r.* of 90:10, respectively (Table 3, Entries 22 and 23).

Table 3: Scope of the catalytic enantioselective difunctionalization of β-perfluoroalkyl enone **1** to $TMSN_3$.[a]



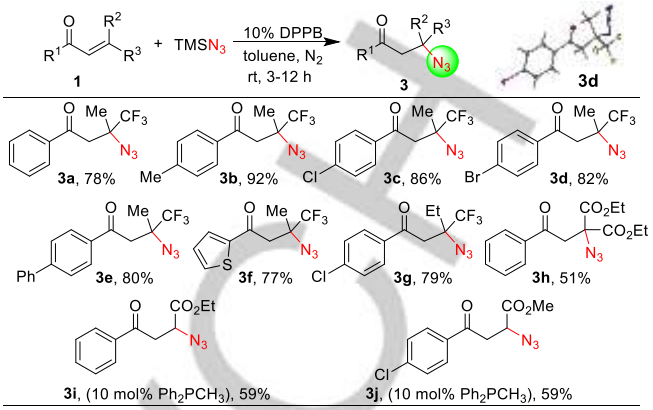
Entry	**1**, R^1/R_f	**(-)-2**, Yield [%][b]	*E.r* [c]
1	**1a**, Ph/CF_3	**(-)-2a**, 88	92.5:7.5
2	**1b**, 4-MeC_6H_4/CF_3	**(-)-2b**, 74	92.5:7.5
3	**1c**, 4-isobutylphenyl/CF_3	**(-)-2c**, 79	92:8
4	**1d**, 4-MeOC_6H_4/CF_3	**(-)-2d**, 74	92.5:7.5
5	**1e**, 4-PhC_6H_4/CF_3	**(-)-2e**, 91	92.5:7.5
6	**1f**, 4-FC_6H_4/CF_3	**(-)-2f**, 82	91:9
7	**1g**, 4-ClC_6H_4/CF_3	**(-)-2g**, 79	91.5:8.5
8	**1h**, 4-Br C_6H_4 /CF_3	**(-)-2h**, 82	91:9
9	**1j**, 4-$F_3CO C_6H_4$/CF_3	**(-)-2j**, 80	87.5:12.5
10	**1k**, 4-$F_3C C_6H_4$/CF_3	**(-)-2k**, 86	86:14
11	**1m**, 4-CNC_6H_4/CF_3	**(-)-2m**, 79	87.5:12.5
12	**1n**, 4-$MeO_2C C_6H_4$/CF_3	**(-)-2n**, 90	91:9
13	**1p**, 4-MeSC_6H_4/CF_3	**(-)-2p**, 69	93:7
14	**1u**, 3,4-$Cl_2C_6H_3$/CF_3	**(-)-2u**, 89	87:13
15	**1w**, 1-naphthy/CF_3	**(-)-2w**, 85	93.5:6.5
16	**1x**, 2-naphthy/CF_3	**(-)-2x**, 76	92.5:7.5
17	**1y**, 2-benzothienyl/CF_3	**(-)-2y**, 63	90.5:9.5
18	**1z**, 2-furyl/CF3	**(-)-2z**, 80	90:10
19	**1da**, Ph/C_2F_5	**(-)-2da**, 86	90:10
20	**1ea**, Ph/C_3F_7	**(-)-2ea**, 88	91:9
21	**1fa,** Ph/CF_2H	**(-)-2fa**, 58	90:10
22[d]	**1a**	**(-)-2a**, 60	89:11
23[e]	**1a**	**(-)-2a**, 65	90:10

[a] Reactions were performed with **1** (0.1 mmol), $TMSN_3$ (0.2 mmol) and **P4** (0.02 mmol) in *o*-xylene (1.0 mL) at room temperture. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $TBSN_3$ instead of $TMSN_3$. [e] $TESN_3$ instead of $TMSN_3$. $TBSN_3$ = azido(tert-butyl)dimethylsilane.

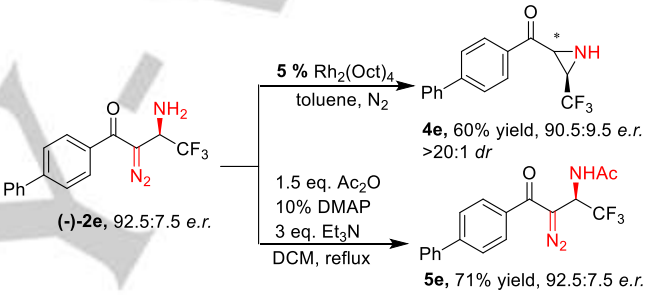
It is very interesting to find that the introduction of the second β-substituent to the β-trifluoromethyl enones would deliver the azide products **3a-3g** in 77-92% yields via the direct conjugate azidation reaction instead of diazo compounds (Table 4). The structure of azide compound **3d** was further sconfirmed by the X-ray single crystal analysis.[9] The reactions of β,β-diester enone and 3-aroyl acrylates also delivered the azide compound rather than the diazo compound with the use of Ph_2PCH_3 as catalyst, indicating the structure of the enones affect the reaction significantly, but the detailed reason is not clear.

Synthetic transformations of the β-amino α-diazocarbonyl compounds were then investigated (Scheme 2). In the presence of $Rh_2(Oct)_4$, the intramolecular N-H insertion reactions of **(-)-2e** proceeded smoothly, delivering the corresponding aziridine products **4e** in 60 yield with *e.r.* of 90.5:9.5. Amino protection of **2e** by Ac_2O in dichloromethane provided the product **5e** in 71% yield with *e.r.* of 92.5:7.5.

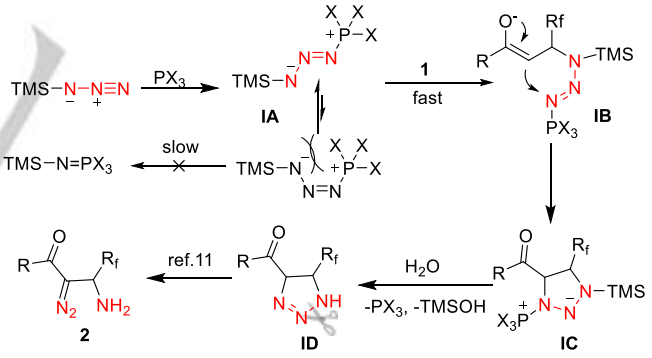
Table 4: Substrate scope of azidation of α,β-unsaturated ketones[a,b].



[a] Reactions were performed with **1** (0.2 mmol), $TMSN_3$ (0.4 mmol), and DPPB (0.02 mmol) in toluene (1.0 mL) at room temperature . [b] Yield of isolated product.



Scheme 2. Synthetic transformations of **(-)-2e**.



Scheme 3. Proposed mechanism.

A plausible reaction mechanism is proposed in Scheme 3. The reaction was initiated by the nucleophilic addition of the phosphine at the terminal nitrogen atom of the azide providing the phosphazide zwitterionic intermediate **IA**. Then the nucleophilic attack of phosphazide zwitterion intermediate **IA** to β-fluoroalkylated α,β-enone **1** results in enolate intermediate **IB**, which intramolecular nucleophilic addition to generate intermediate **IC**. Subsequent β-elimination of the phosphine catalyst and hydrolysis[10] leads to the cycloadduct **ID**, which rapidly undergoes further fragmentation[11] to give the final β-amino α-diazocarbonyl compounds.

To gain insight the reaction pathway, some control experiments (Supporting Information, Figure **S1**) and a series of experiments monitored by ^{19}F NMR spectroscopy and ^{31}P NMR (Fig. **S2**-**S4**) were carried out. The substrate **1g** alone showed a ^{19}F resonance signal at -64.85 ppm and the product **2g** alone showed a ^{19}F resonance signal at -77.17 ppm. When mixing

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dppb with $TMSN_3$ and **1g** in toluene-d_8 within 10 mins, three new resonance appeared at -73.16, -75.28, -77.17 ppm. After 3 hours, the peaks at -64.85 ppm (from **1g**), -73.16 ppm disappeared and the peak at 75.28 ppm becomes smaller. This result suggests that -73.16 ppm and -75.28 are most likely the reaction intermediates. The key reaction intermediates were then detected by ESI-MS (Fig. **1**), which is a direct and reliable method for the characterization of reaction intermediates in situ.[12] When the reaction mixed DPPB and $TMSN_3$ in DCM was monitored, an ion of m/z 542 was obtained (Fig. **1a**), indicating the existence of intermediate **IA**. The SAESI-MS/MS spectrum of the reaction mixture of **1g**, $TMSN_3$ and PPh_3, exhibits the peak at m/z 612 (Fig. **1b**) and m/z 350 (Fig. **S7**), which support the structures of intermediates **IB** or **IC** and **ID**.

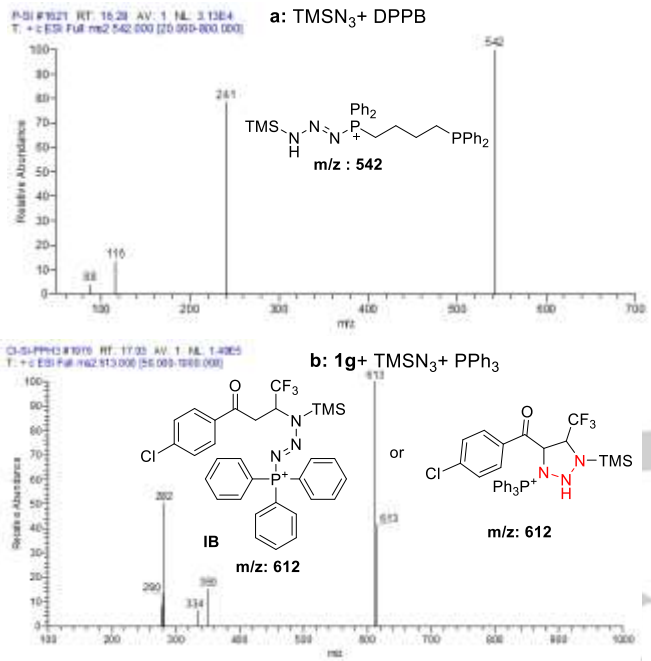

Figure 1. **ESI-MS studies:** a) SAESI-MS spectrum of the reaction solution in DCM, showing the complex ion $[TMSN_3(DPPB)+H]^+$ at *m/z* 542. b) The SAESI-MS/MS spectrum of $[C_{31}H_{31}ClF_3N_3OPSi]^+$ at *m/z* 612.

In summary, we have developed a novel strategy for phosphine-catalyzed difunctionalization of α,β-enones under the mild reaction conditions. In particular, it is the first example of construction of α-diazo carbonyl compounds under phosphine catalysis conditions. In contrast, the corresponding β-azide compounds would be furnished with the use of β,β-disubstituted enones or 3-aroyl acrylates via the direct monofunctionalization (azidation) reaction. Furthermore, a preliminary result showed that an asymmetric variant of the reaction has also been realized with quite high enantioselectivities with the use of nucleophilic bifunctional phosphine **P4** as a chiral catalyst, which providing a facile access to various functional fluoroalkylated β-amino α-diazocarbonyl compounds. Mechanistic studies shed some light on the mode of catalyst activation and intermediate formation. ESI-MS studies were carried out to detect the reaction intermediates to explain the process.

Acknowledgements

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Keywords: phosphine catalysis• alkene difunctionalization• diazo compounds• azide •enones

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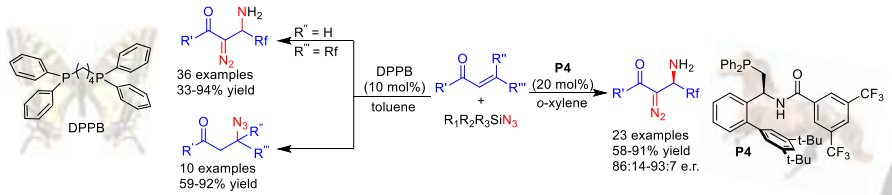

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Phosphine-Catalyzed Difunctionalization of α,β-Enones: A Direct Approach to β-Amino α-DiazoCarbonyl Compounds

An efficient and practical phosphine-catalyzed vicinal difunctionalization of β-fluoroalkyl α,β-enones with $TMSN_3$ has been developed. Meanwhile, the asymmetry variant induced by the nucleophilic bifunctional phosphine **P4** led to various chiral fluoroalkylated β-amino α-diazocarbonyl compounds in high yields and enantioselectivity.