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Efficient approaches for the synthesis of diverse α-diazo amides

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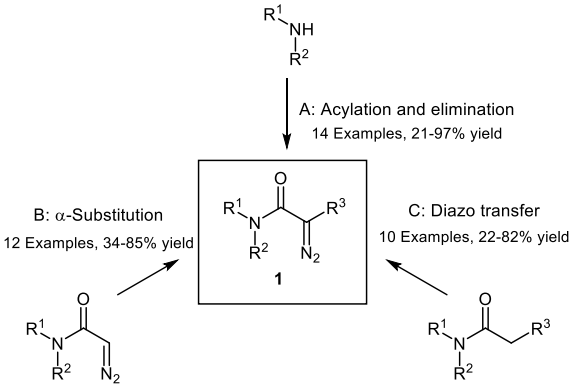

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Abstract Metal-catalysed carbenoid chemistry may be exploited in the synthesis of diverse range of small molecules from α-diazo carbonyl compounds. In this paper, three synthetic approaches to α-diazo amides have been developed, and their scope and limitations have been determined. On the basis of these synthetic studies, recommendations are provided to assist the selection of the most appropriate approach for specific classes of product. The availability of practical and efficient syntheses of diverse α-diazo acetamides is expected to facilitate the discovery of many different classes of bioactive small molecules.

Key words diazo compounds; molecular diversity; carbenoid chemistry

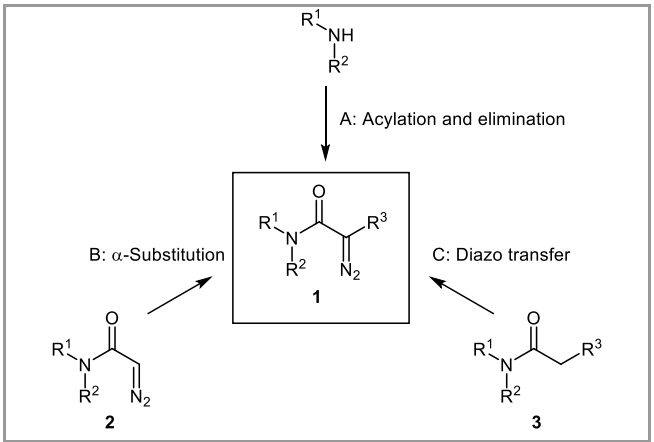
Introduction

Metal-catalysed carbenoid chemistry can enable the synthesis of many different classes of small molecule.[1] The diversity of the possible products stems from the many different patterns of reactivity that are possible, and the scope for both inter- and intramolecular reactions. The diverse patterns of possible reactivity include insertion into C–H, O–H and N–H bonds, cyclopropanation and ylide formation; some of these processes also enable subsequent chemistry such as cycloaddition or rearrangement reactions.[2-4] Crucially, judicious choice of catalyst can provide control over stereochemistry, chemoselectivity (e.g. which C–H bond in a complex substrate) and reaction fate (e.g. which mode of reactivity is favoured).[5-10] The diversity of possible reaction outcomes can enable the parallel discovery of diverse bioactive chemotypes.[11,12]

We therefore investigated a suite of methods for the synthesis of α-diazo amides and some related compounds. These methods would ideally enable the efficient synthesis of structural-diverse diazo compounds from readily-available substrates without the need for purification of any intermediates. Overall, the developed methods would ideally be complementary, and enable the efficient synthesis of a diverse range of substrates.

Results and discussion

We envisaged three general synthetic approaches to α-diazo amides **1** (Scheme 1): acylation with an appropriate reagent followed by elimination (Approach A); α-substitution of α-diazo acetamides **2** (Approach B); and diazo transfer (Approach C). Here, we describe the development, and demonstration of the scope and limitations of, practical methods for the synthesis of α-diazo amides (and some related compounds) from readily-available starting materials.

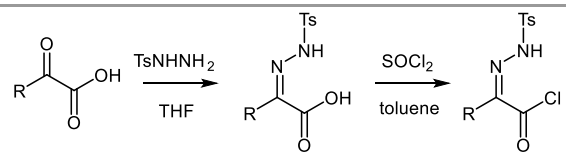


Scheme 1 Overview of synthetic approaches to α-diazo amides.

Approach A: Synthesis by acylation and elimination

We developed a one-pot synthesis of α-diazo amides from readily-available amines that was based on an established synthesis of α-diazoacetic esters.[13,14] Glyoxylic acid **4a** and phenylglyoxylic acid **4b** were converted into the corresponding toluenesulfonyl hydrazones **5**; treatment with thionyl chloride in toluene at 90 °C gave the corresponding acid chlorides **6** which were used without purification (Scheme 2). The acid chlorides **6a** and **6b** were orange and yellow amorphous solids

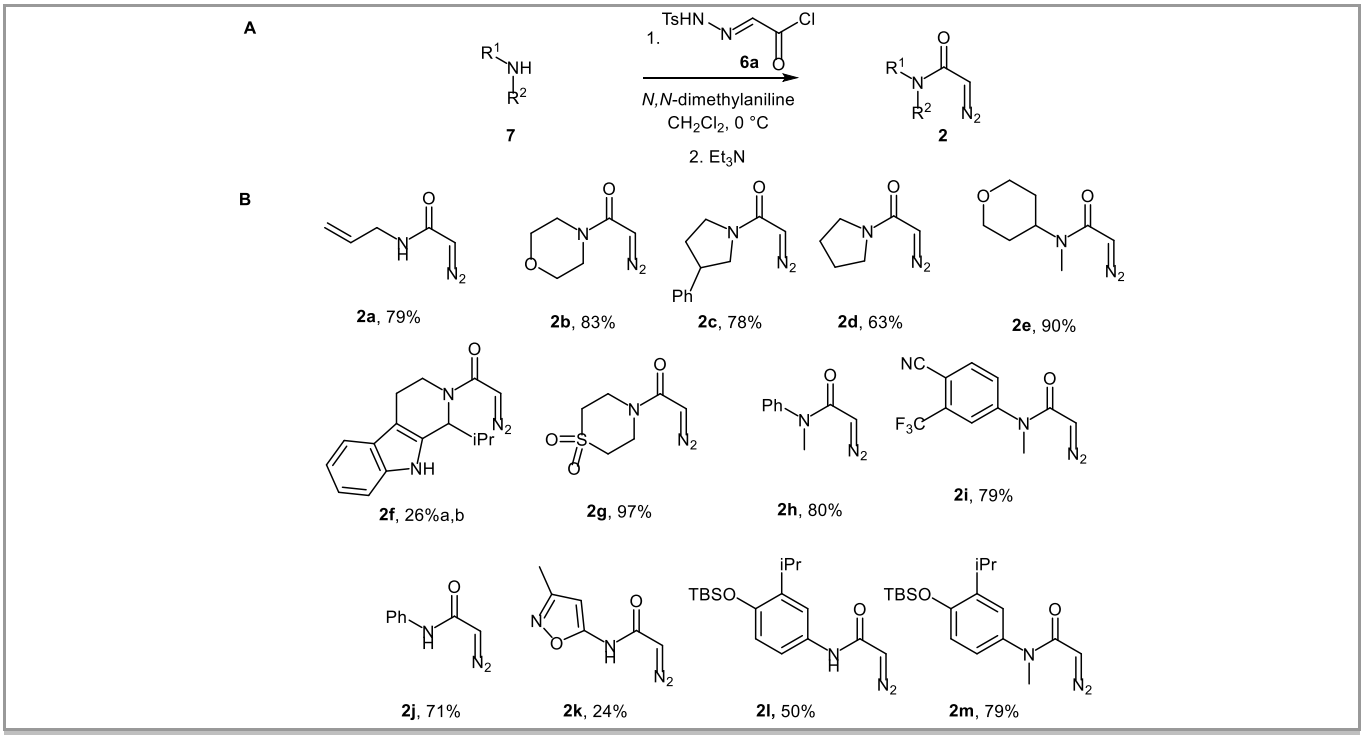
respectively, and were stored in vacuo at room temperature for a maximum of 12 hr prior to use.



Scheme 2 Synthesis of the acid chlorides **6** which were used without purification.

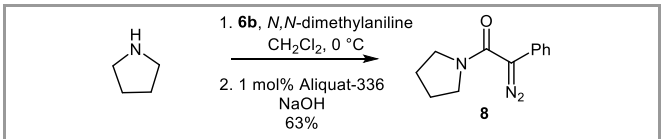
The acid chloride **6a** was exploited in the synthesis of α-diazo acetamides. Accordingly, a solution of the acid chloride **6a** in dichloromethane at 0 °C was treated with the requisite amine and *N,N*-dimethylaniline under a nitrogen atmosphere; after 2 hr, triethylamine was added to induce elimination to yield the corresponding α-diazo acetamide (Scheme 3). Although DBU has been used in syntheses of related products,[15] we found triethylamine enabled more facile product purification.

The approach enabled the synthesis of a wide range of α-diazo acetamides. In particular, a primary amine (→ **2a**), secondary amines (→ **2b-g**) and anilines / hetarylamines (→ **2h-m**) were successful as substrates. In the case of sterically-hindered secondary amines, prolonged coupling and/or elimination was necessary to yield the corresponding α-diazo acetamides (e.g. **2f**). The α-diazo acetamides **2a-2m** were stored at −20 °C; under these conditions, the α-diazo acetamide **2h**, for example, was spectroscopically identical after storage for more than a year.



Scheme 3 One-pot synthesis of α-diazo acetamides. Panel A: General synthetic scheme. Panel B: Structures of the α-diazo acetamides prepared. [a]Prolonged reaction (24 hr) between the amine and the acid chloride was required. [b]Prolonged reaction time (48 hr) for the elimination was required.

The acid chloride **6b** was exploited in the synthesis of an α-diazo α-phenyl acetamide (Scheme 4). After coupling with pyrrolidine (3.3 eq.) in the presence of *N,N*-dimethylaniline, elimination was induced by treatment with a 12 M aqueous solution of sodium hydroxide and the phase transfer catalyst trioctylmethylammonium chloride (Aliquat® 336; 1 mol%). We had investigated the use of trimethylamine and DBU in the elimination step with little success, even at elevated temperature, before arriving at these optimal conditions.[16] We demonstrated that, with pyrrolidine, good yields of the corresponding α-diazo α-phenyl acetamide **8** could be obtained.



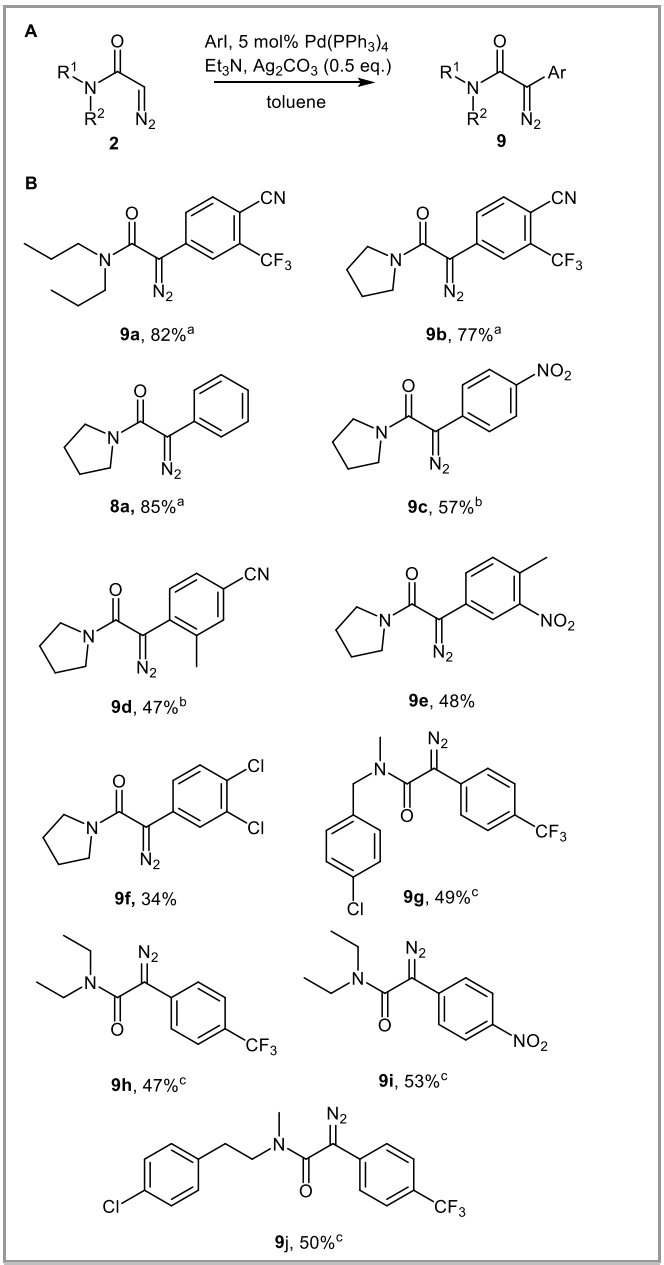
Scheme 4 One-pot synthesis of a α-diazo α-phenyl acetamide.

Approach B: Synthesis by α-arylation of the corresponding α-diazo acetamide

We developed a method for the α-arylation of α-diazo acetamides **2** (Scheme 5).[17] The beneficial effect of Ag_2CO_3 was found following a limited additive screen, and is in line with previous studies involving related substrates.[17b] In each case, $Pd(PPh_3)_4$ (5 mol%) and Ag_2CO_3 (0.5 equiv.) were placed in oven-dried glassware under a nitrogen atmosphere, and anhydrous toluene, the aryl halide (1 eq.), triethylamine and a

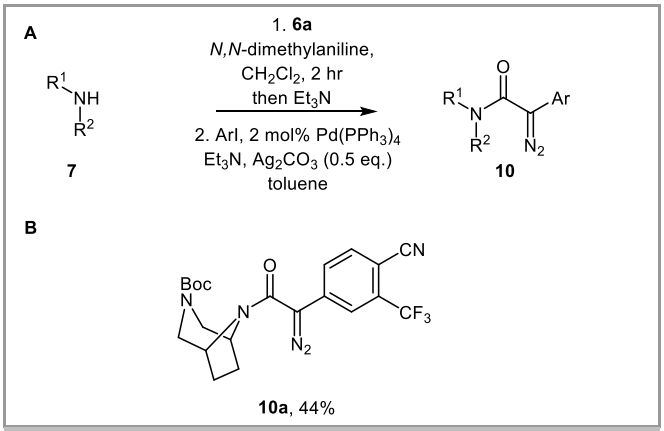
solution of the α-diazo acetamide **2** (1.3 eq.) in anhydrous toluene were added sequentially. The reactions were stirred at room temperature, generally for 4 hr.

The demonstrated scope of the method is shown in Scheme 5 (Panel B). Couplings were successful with a wide range of aryl iodides including iodobenzene (→ **8a**) and electron-deficient (e.g. → **9a**, **9b** and **9e-i**) substrates; it was found that couplings proceeded most rapidly with electron-deficient substrates. Couplings with 5-iodoindole and 4-iodoanisole showed slow conversion by TLC and, despite extended (48 hr) reaction times, product purification was difficult due to the poor conversions. In addition, couplings with aryl bromides were successful with electron-deficient substrates (e.g. → **9c** and **9d**): however, there was no evidence of conversion by TLC with bromobenzene, 1-bromo-3-methoxybenzene, 1-bromo-4-methoxybenzene or 3-bromopyridine, even with extended reaction times.



Scheme 5 Palladium-catalysed synthesis of α-aryl α-diazo acetamides. Panel A: General synthetic scheme. Panel B: α-Aryl α-diazo acetamides prepared. [a]Prepared by method B2, with a 1:1 stoichiometry of diazo to aryl iodide. [b]Prepared from the corresponding aryl bromide. [c]Prepared from α-diazo acetamides described in the ESI.

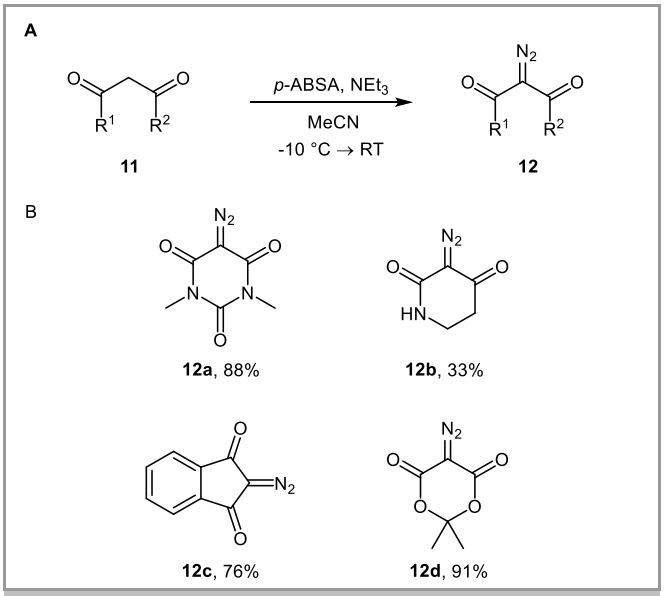
We also developed a procedure in which the synthesis of the α-diazo acetamide was telescoped with subsequent α-arylation (Scheme 6). The telescoped procedure was successful with a bridged secondary amine as a substrate (→ **10a**).



Scheme 6 Telescoped synthesis of α-aryl α-diazo acetamides from amines and a lactam. Panel A: General synthetic scheme. Panel B: α-Aryl α-diazo acetamides prepared.

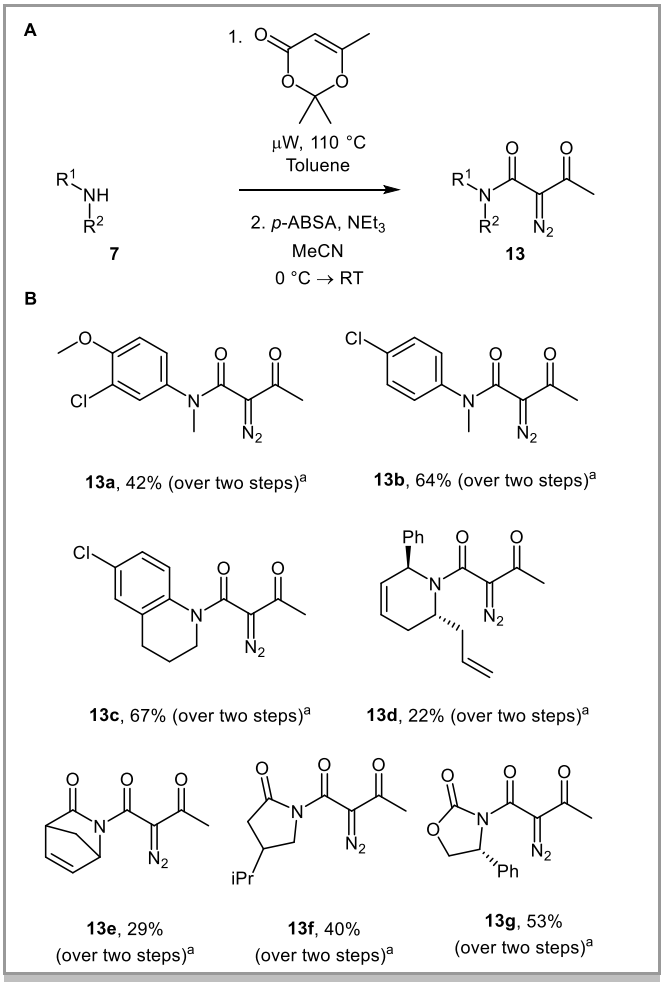
Approach C: Synthesis by diazo transfer

The synthesis of α-diazo carbonyl compounds by diazo transfer has been demonstrated with a range of substrate classes.[18,19] We initially adopted this approach with cyclic 1,3-dicarbonyl compounds (Scheme 7). In our preliminary studies, we had found that the use of triethylamine as the base, rather than DBU, enabled more facile product purification. Accordingly, triethylamine (1.2 eq.) was added dropwise to a solution of the appropriate 1,3-dicarbonyl compound and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.5 eq.) in anhydrous acetonitrile at –10 °C, and the reaction then stirred at room temperature. Under these optimal conditions, diazo transfer was rapid and was accompanied by precipitation of 4-acetamidobenzenesulfonamide.[20] Efficient diazo transfer was observed with a range of 1,3-dicarbonyl compounds including 1,3-dimethyl barbituric acid (→ **12a**), a β-keto lactam (→ **12b**), a 1,3-diketone (→ **12c**) and Meldrum's acid (→ **12d**).



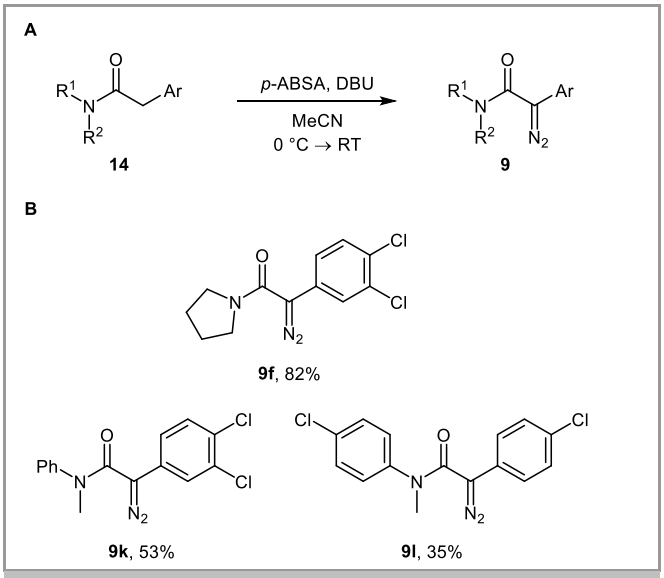
Scheme 7 Diazo transfer with cyclic 1,3-dicarbonyl substrates.

We also investigated the diazo transfer reactions of acyclic β-keto amides (Scheme 8). A range of structurally diverse β-keto amide derivatives was prepared by reaction of the appropriate nitrogen nucleophile with 2,2,6-trimethyl-1,3-dioxin-4-one (1.1 eq.) under microwave irradiation (110 °C, max 200 W, max 300 psi) for 1.5-2 hr.[21] Our previous experience[11,12] had shown that it was possible to telescope the acylation step with a subsequent diazo transfer reaction. Accordingly, treatment of the crude acylation products and *p*-ABSA with triethylamine at 0 ºC resulted in smooth diazo transfer. Significantly extended reaction times (20-24 hr) were required to yield the diazo products **13d**, **13f** and **13g**. Remarkably, the approach was successful with a wide range of nitrogen nucleophiles including anilines (→ **13a-c**), a secondary amine (→ **13d**), lactams (→ **13e** and **13f**) and an oxazolidinone (→ **13g**).



Scheme 8 Synthesis of α-diazo β-keto amides by diazo transfer. Panel A: General synthetic scheme. Panel B: α-Diazo β-keto amides prepared. [a]Telescoped yield.

The synthesis of α-aryl α-diazo acetamides **9** by diazo transfer was also investigated (Scheme 9). Although similar α-aryl α-diazo acetamides **9** had previously been prepared using diphenyl phosphoryl azide (DPPA) and LDA,[22] we recognised the advantages of *p*-ABSA in terms of both safety and ease of product purification. We found DBU to be an effective base for the transformation. Accordingly, DBU (2 eq.) was added dropwise to a solution of the appropriate α-aryl acetamide and *p*-ABSA (1.1 eq.); the reactions were allowed to warm to room temperature over 4 hr. The method was successful with α-aryl acetamides derived from both anilines (→ **9k** and **9l**) and a secondary amine (→ **9f**).



Scheme 9 Synthesis of α-aryl α-diazo acetamides by diazo transfer. Panel A: General synthetic scheme. Panel B: α-Aryl α-diazo acetamides prepared.

Conclusions

α-Diazo amides have diverse reactivity that can be harnessed in the synthesis of a wide range of molecular scaffolds. Indeed, we have previously exploited metal-catalysed reactions of α-diazo amides in the activity-directed synthesis of diverse androgen receptor agonists. The scope of three synthetic approaches was determined, and a summary of our recommendations for which approach is most suitable specific classes of product is provided in Figure 1.

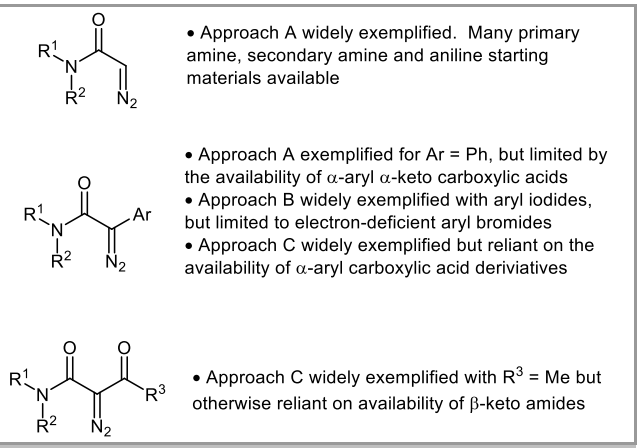


Figure 1 Scope of the approaches for the synthesis of α-diazo amides. Approach A: Synthesis by acylation and elimination. Approach B: Synthesis by α-arylation of the corresponding α-diazo acetamide. Approach C: Synthesis by diazo transfer.

We demonstrated that Approach A (Synthesis by acylation with an acid chloride **6** and subsequent elimination) enables the synthesis of a wide range of α-diazo acetamides. The value of the approach is likely to be very high because of the very wide availability of primary amine, secondary amine and aniline substrates.

All three of the approaches can enable the synthesis of α-aryl α-diazo amides. The poor availability of α-aryl α-keto carboxylic acids means that Approach A is likely to be most useful for the synthesis of phenyl-substituted analogues. Approach B (Synthesis by Pd-catalysed α-arylation of α-diazo acetamides), on the other hand, enables the introduction of a very broad range of (het)aryl substituents. However, although many aryl iodides are competent substrates, the scope of the approach is less broad with (more generally available) aryl bromides. Finally, Approach C (Synthesis by diazo transfer) is successful with a range of α-aryl acetamides and enables the synthesis of a wide range of α-diazo β-keto amides. The approach is particularly valuable for α-diazo β-keto butanamides because the required substrates may be easily prepared by acylation of the appropriate nitrogen nucleophile (including amines, anilines, lactams and oxazolidinones).

Overall, the availability of practical and efficient approaches for the synthesis of α-diazo acetamides is expected to facilitate the discovery of diverse bioactive small molecules.

Experimental

CAUTION: Diazo compounds are potentially explosive and must be handled with care. For concentration of material under reduced pressure, a maximum water bath temperature of 40 ºC was used. Contact with metal was avoided during syntheses. No problems were encountered during our synthetic studies on the scales that are described below.

All non-aqueous reactions were carried out under an atmosphere of nitrogen unless otherwise stated and water-sensitive reactions were performed in anhydrous solvents (obtained from a PureSolv MD5 Purification System) in oven-dried glassware and cooled under nitrogen before use. All other solvents and reagents were of analytical grade and used as supplied. Ether refers to diethyl ether and petrol refers to petroleum spirit (b.p. 40-60 °C) unless otherwise stated. Solvents were removed under reduced pressure using an IKA RV 10 rotary evaporator. General procedures B2 and C3 are included in the Supporting Information.

Flash column chromatography was carried out using silica gel 60 (35-70 μm particles) supplied by Merck. Thin layer chromatography was carried out using commercially available pre-coated aluminium plates (Merck silica gel 60 F254). Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualisation.

Accurate mass spectrometry was performed using electrospray ionisation on a Bruker MaXis Impact spectrometer. ^1H and ^{13}C NMR spectra were collected on a Bruker Advance 500, Bruker DPX500, DPX400 or DPX300 spectrometer using an internal deuterium lock. NMR spectra were recorded at 300 K, unless otherwise stated. Chemical shifts are quoted in parts per million down field of trimethylsilane and coupling constants (*J*) are given in Hz. Infrared spectra were recorded on a Bruker Alpha ATR FR-IR spectrometer; absorptions are reported in wavenumber (cm^{-1}).

General Procedure A: **Synthesis of diazo compounds using acid chloride reagent**

Toluenesulfonoyl hydrazone, **5a** or **5b**, (1 eq.) was dissolved in anhydrous toluene (25 mL) and purged with N_2 for 5 min. Thionyl chloride (2 eq.) was added dropwise at RT and the solution was stirred vigorously and slowly heated to 90 °C over 30 min. After 4 hr, the reaction mixture was cooled to RT, the

solvent was removed under reduced pressure and the crude product was dried under vacuum.

The crude product (1 eq.) was dissolved in anhydrous CH_2Cl_2 (3 mL/mmol) and cooled to 0 °C. A solution of amine (2 eq.) in CH_2Cl_2 (0.5 mL/mmol) and a separate solution of dimethylaniline (1 eq.) were added slowly under an N_2 atmosphere. The reaction mixture was stirred overnight before NEt_3 (5 eq.) was added dropwise over 10 min. The reaction mixture was allowed to return to RT gradually and the solution was stirred overnight. The reaction mixture was washed with aqueous sodium bicarbonate solution and brine solution successively. The organic layer was collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude diazo amide.

General Procedure B1:

The appropriate diazo compound (1.3 eq) as a solution in dry PhMe, was added to a stirred suspension of the appropriate ArI (1 eq), $Pd(PPh_3)_4$ (5 mol%), Ag_2CO_3 (0.5 eq), and NEt_3 (1.3 eq) in dry PhMe under an N_2 atmosphere. The syringe was washed twice with dry PhMe and the washings were added to the reaction mixture for a final conc. of 0.25 M. After 4 hr, the reaction mixture was filtered through a silica plug (2 × ø2 cm) eluting with EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure to give a crude product and was purified by flash column chromatography.

General Procedure C1: Synthesis of diazo compounds by diazo transfer

A solution of dicarbonyl compound (1 eq.) and *p*-ABSA (1.5 eq.) in anhydrous MeCN was cooled to -10 °C. NEt_3 (1.2 eq.) was added dropwise over 5-10 min and the mixture was stirred at RT under a N_2 atmosphere. After 0.5-1 hr (when a solid precipitated out of solution and the starting material had been consumed by TLC), the solvent was removed under reduced pressure and the crude product was dissolved in Et_2O (30 mL/mmol), filtered and the resulting solid rinsed with CH_2Cl_2 (30 mL/mmol). The filtrate was concentrated and purified by flash column chromatography.

General Procedure C2: Synthesis of diazo compounds by acylation followed by diazo transfer

2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (1.1 eq.) was added to a solution of aniline (1 eq.) in toluene and the mixture was reacted under μW irradiation (110 °C, max 200 W, max 300 psi). After 1.5-2 hr, the solvent was removed under reduced pressure. *p*-ABSA (1.5 eq.) was added followed by anhydrous MeCN and the solution was cooled to 0 °C. NEt_3 (1.2 eq.) was added dropwise over 5-10 min and the mixture was stirred at RT under an N_2 atmosphere. After 4 hr, the solvent was removed under reduced pressure and the crude product purified by flash column chromatography.

2-(4-Methylbenzenesulfonamido)imino acetic acid, 5a

Glyoxylic acid (0.08 mol, 7.4 g) and *p*-toluenesulfonylhydrazide (0.05 mol, 10.0 g) were dissolved in THF (70 mL) and the mixture stirred vigorously at RT for 24 hr. The solvent was removed under reduced pressure and the resulting residue was triturated with cold water. The solid was air-dried for two days to attain the crude product. The crude product was recrystallised in EtOAc to afford pure product **5a** as a white amorphous solid (12.80 g, 99%); ^{1}H (400 MHz, Acetone-d_6): δ = 11.01 (1H, s, OH), 7.82 (2H, d, J 8.0, phenyl 3-H and 5-H), 7.43 (2H, d, J 8.0, phenyl 2-H and 6-H), 7.32 (1H, s, 2-H) and 2.42 (3H, s, Methyl); δc (100 MHz, Acetone-d_6) 206.3, 163.8, 145.3, 137.3, 130.6, 128.5 and 21.4; IR ν_{max} (neat)/cm^{-1} 3170, 2892, 1695 and 1595; HRMS (ESI) $C_9H_{10}N_2NaO_4S$ requires [M+Na]+, calculated 265.0254, found 265.0252.

2-Diazo-N-(prop-2-en-1-yl)acetamide, 2a

By general procedure A, **6a** (3 mmol, 780 mg) with allylamine (6 mmol, 448 μL) gave a crude material and was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2a** as a yellow oil (298 mg, 79%); R_f 0.40 (Et_2O); IR ν_{max}/cm^{-1} (film) 3291, 3089, 2925, 2103, 1618 and 1542; ^{1}H (400 MHz, Acetone-d_6) δ = 6.91 (1H, br s, NH), 5.85 (1H, ddt, J 17.2, 10.6 and 5.4, propenyl 2-H), 5.72 (1H, s, diazoacetamide 2-H1), 5.16 (1H, dq. J 17.2 and 1.6, propenyl 3-H trans), 5.04 (1H, dq, J 10.3 and 1.6, propenyl 3-H cis) and 3.86 (2H, tt, J 5.7 and 1.6, propenyl 1-H); 13C (100 MHz, Acetone-d_6): δ = 165.7, 136.4, 115.5, 46.8 and 42.5; HRMS (ESI): $C_{10}H_{14}N_6O_2Na$ requires [2M+Na]+, calculated 273.1076 found 273.1069.

2-Diazo-1-(morpholin-4-yl)ethenone, 2b

By general procedure A, **6a** (1.5 mmol, 390 mg) and morpholine (3 mmol, 260 μL) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2d** as a yellow oil (193 mg, 83%); R_f 0.24 (Et_2O); IR ν_{max}/cm^{-1} (film) 3056, 2973, 2036, 1647, 1488; ^{1}H (300 MHz, Acetone-d_6): δ = 5.34 (1H, s, diazo acetamide 2-H1), 3.30 (4H, app br m, morpholine 2-HAB and 6-HAB) and 1.89 (4H, app br s, morpholine 3-HAB and 5-HAB); ^{13}C (75 MHz, Acetone-d_6): δ = 164.0, 46.4, 26.5 and 25.2. HRMS (ESI): $C_6H_{10}N_3O_2$ requires [M+H]+, calculated 156.0773, found 156.0768.

2-Diazo-1-(3-phenylpyrrolidin-1-yl)ethan-1-one, 2c

By general procedure A, **6a** (3.4 mmol, 884 mg) and 3-phenyl pyrrolidine (6.8 mmol, 1 g) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2 for three column volumes then CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2e** as a bright orange oil (574 mg, 78%); R_f = 0.32 (Et_2O); IR ν_{max} (CH_2Cl_2 film)/cm^{-1} 2095, 1600, 1417, 1166; ^{1}H (500 MHz, CD_2Cl_2): δ = 7.33 (2H, dd, *J* 7.0, 8.0), 7.26 (3H, m), 4.89 (1H, s), 4.02-3.62 (2H, m), 2.35-2.29 (1H, broad m), 2.07-2.01 (1H, broad m); ^{13}C (125 MHz, CD_2Cl_2): δ = 163.8 (rot-A/B), 141.4 (rot-B), 141.1 (rot- A), 129.9 (rot-B), 129.8 (rot-A), 128.7 (rot-A/B), 127.14 (rot-A/B), 52.5 (rot-A/B), 52.3 (rot-A/B), 46.2 (rot-A), 45.8 (rot-B), 44.6 (rot-A), 42.9 (rot-B), 33.4 (rot-A), 33.1 (rot-B); HRMS (ESI): $C_{12}H_{13}N_3O$ requires $[M+H]^+$, calculated 216.1137, found 216.1127.

2-Diazo-1-(pyrrolidin-1-yl)ethenone, 2d

By general procedure A, **6a** (1.5 mmol, 390 mg) and pyrrolidine (3 mmol, 246 μL) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2f** as a yellow oil (132 mg, 63%); R_f = 0.20 (Et_2O); IR ν_{max} (neat)/cm^{-1} 3063, 2974, 2875, 2096, 1594 and 1425; ^{1}H (400 MHz, $CDCl_3$): δ = 4.80 (1H, s, diazoacetamide 2-H), 3.52 (2H, app br s, pyr 2-H_A and 5-H_A), 3.20 (2H, app br s, pyr 2-H_B and 5-H_B),), 1.94 (2H, app br s, pyr 3-H_A and 4-H_A) and 1.87 (2H, app br s, pyr 3-H_B and 4-H_B); ^{13}C (100 MHz, $CDCl_3$): δ = 163.2, 63.2, 45.5, 17.8 and 14.8; HRMS (ESI): $C_6H_9N_3O$ requires $[M+Na]^+$, calculated 162.0643, found 162.0638.

2-Diazo-*N*-methyl-*N*-(oxan-4-yl)acetamide, 2e

By general procedure A, **6a** (4.3 mmol, 1.12 g) and *N*-methyl-*N*-tetrahydro-2H-pyran-4-ylamine (4.3 mmol, 495 mg) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) for 3 column volumes then Et_2O to afford the *diazo acetamide* **2h** as a bright orange oil (708 mg, 90%); R_f = 0.10 (Et_2O); IR ν_{max} (CH_2Cl_2 film)/cm^{-1} 2098, 1600, 1410, 1256, 1144 and 1086; ^1H (500 MHz, CD_2Cl_2): δ = 5.01 (1H, s), 3.98 (1H, d, *J* 4.6), 3.96 (1H, d, *J* 4.6), 3.44 (2H, t, *J* 11.4), 2.7 (3H, s), 1.77-1.73 (3H, m) and 1.55-1.52 (2H, m). ^{13}C (125 MHz, CD_2Cl_2): δ = 165.9 (rot-A/B), 130.0 (rot-A), 126.6 (rot-B), 104.6 (rot-A/B), 67.8 (rot-A/B), 46.8 (rot-A/B) and 30.7 (rot-A/B); HRMS (ESI): $C_8H_{13}N_3O_2$ requires $[M+Na]^+$, calculated 206.0905, found 206.0892.

2-Diazo-1-(2-isopropyl-2,5-dihydropyrrol-1-yl)ethenone, 2f

By general procedure A, **6a** (6 mmol, 1.56 g) and 2-isopropyl-2,5-dihydro-1H-pyrrole (12 mmol, 1.55 mL) gave a crude material and was purified by flash column chromatography eluting with Petrol–EtOAc (8:2) to give the *diazo acetamide* **2i** as a yellow oil (0.225 g, 21%); R_f = 0.31 (Petrol–EtOAc, 8:2); IR ν_{max} (film)/cm^{-1} 2961, 2100, 1700, 1596 and 1412; ^1H (300 MHz, Acetone-d_6): δ = 5.93 (1H, m, dihydropyrrolyl 4–H), 5.83 (1H, m, dihydropyrrolyl 3–H), 5.40 (1H, s, 2–H), 4.71 (1H, m, dihydropyrrolyl 2–H), 4.06 (2H, m, dihydropyrrolyl 5–H), 2.49 (1H, m, isopropyl–H), 0.92 (3H, d, *J* 6.7, isopropyl–H^a) and 0.69 (3H, d, *J* 6.7, isopropyl–H^b); ^{13}C (75 MHz, Acetone-d_6): δ = 164.5, 127.9, 126.8, 70.6, 54.9, 46.8, 30.6, 19.2 and 16.0; HRMS (ESI) $C_9H_{13}N_3ONa$ requires $[M+Na]^+$, calculated 202.0951, found 202.0946.

2-Diazo-1-{1-isopropyl-1H,3H,4H,9H-pyrido[3,4-b]indol-2-yl}ethenone, 2g

By general procedure A, **6a** (6.2 mmol, 1.61 g) and 1-isopropyl-1H,2H,3H,4H,9H-pyrido[3,4-b]indole (12.4 mmol, 2.66 g) gave a crude material and was purified by flash column chromatography, eluting with CH_2Cl_2–MeOH (99:1) to give the *diazo acetamide* **2j** as a yellow amorphous solid (0.457 g, 26%); IR ν_{max} (film)/cm^{-1} 3194, 2967, 2103, 1580, 1467, 1428, 1349; ^1H (300 MHz, CD_2Cl_2): δ = 7.48 (1H, d, *J* 7.5, indolyl 5–H), 7.36 (1H, d, *J* 7.5, indolyl 8–H), 7.14 (2H, m, indolyl 6–H and 7–H), 5.58 (1H, d, *J* 14.4, indolyl 1–H), 5.25 (1H, s, 2–H), 3.50 (2H, br m, indolyl 3–H), 2.82 (2H, m, indolyl 4–H), 2.14 (1H, dt, *J* 6.7, 6.7 and 14.4, isopropyl–H), 1.15 (3H, d, *J* 6.7, isopropyl–H^a), 0.99 (3H, d, *J* 6.7, isopropyl–H^b); ^{13}C (126 MHz, methylene chloride-d_2): δ = 166.1, 136.7, 134.7, 127.1, 121.9, 119.5, 118.2, 111.6, 107.7, 56.2, 47.1, 41.2, 33.7, 22.3, 20.2, 20.1; R_f 0.39 (CH_2Cl_2–MeOH, 99:1); HRMS (ESI) $C_{16}H_{18}N_2O$ requires $[M-N_2]$, calculated 254.1414, found 254.1486.

4-(Diazoacetyl)-1-thiomorpholine-1,1-dione, 2h

By general procedure A, **6a** (1.5 mmol, 390 mg) and thiomorpholine-1,1-dioxide (3 mmol, 405 mg), gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2k** as a yellow solid (295 mg, 97%); R_f 0.34 (Pentane–Et_2O, 1:1); ^1H (400 MHz, Acetone-d_6): δ = 5.88 (1H, s, diazoacetamide 2-H), 3.92 (4H, m, 2-H_{AB} and 6-H_{AB}) and 3.10 (4H, m, 3-H_{AB} and 5-H_{AB}); ^{13}C (100 MHz, Acetone-d_6): δ = 165.6, 52.42, 46.9 and 43.2; HRMS found MNa^+: 226.0255 ($C_6H_9N_3O_3SNa$ *requires MNa*, 226.0262).

2-Diazo-*N*-methyl-*N*-phenylacetamide, 2i

By general procedure A, **6a** (3 mmol, 780 mg) and *N*-methylaniline (6 mmol, 650 μL) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2l** as an orange oil (419 mg, 80%); R_f = 0.45 (Pentane–Et_2O, 1:1); IR ν_{max} (neat)/cm^{-1} 3118, 3061, 2934, 2101 and 1621; ^1H (400 MHz, $(CD_3)_2CO$): δ = 7.48-7.28 (2H, m, Ar 3-H and 5-H), 7.28-7.18 (1H, m, Ar 4-H), 7.20-7.16 (2H, m, Ar 2zz-H and 6-H), 4.81 (1H, s, diazoacetamide 2-H) and 3.12 (3H, s, *N*Me); ^{13}C (100 MHz, $(CD_3)_2CO$): δ = 165.7, 144.4, 130.5, 128.4, 128.2, 47.4 and 37.1; Spectroscopic data matches literature [23]

***N*-[4-Cyano-3-(trifluoromethyl)phenyl]-2-diazo-*N*-methylacetamide, 2j**

By general procedure A, **6a** (1 mmol, 260 mg) and *N*-methyl-4-cyano-3-trifluoromethylaniline (2 mmol, 400 mg), a crude material was obtained and purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **2o** as a yellow solid (212 mg, 79%); R_f 0.43 (Et_2O); ^1H (400 MHz, $(CD_3)_2CO$): δ = 8.11 (1H, d, *J* 8.4, Ar 5-H), 8.05 (1H, d, *J* 2.0, Ar 2-H), 7.89 (1H, dd, *J* 8.4 and 2.0, Ar 6-H), 5.56 (1H, s, diazoacetamide 2-H), 3.40 (3H, s, *N*Me); ^{13}C (101 MHz, $(CD_3)_2CO$): δ = 166.4, 148.9, 137.0, 130.4, 125.2, 125.1, 116.0, 48.7, 36.8; IR ν_{max} (neat)/cm^{-1} 3091, 2231, 2108, 1605, 1377; HRMS (ESI): $C_{11}H_8F_3N_4O$ requires $[M+H]^+$, calculated 269.0690, found 269.0619. Spectroscopic data matches literature [12]

2-Diazo-*N*-phenylacetamide, 2k

By general procedure A, **6a** (3 mmol, 780 mg) and aniline (6 mmol, 545 μL), a crude material was obtained and purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the diazo acetamide **2p** as an orange solid (682 mg, 71%); R_f = 0.52 (CH_2Cl_2–Et_2O, 9:1); ^1H (400 MHz, Acetone-d_6): δ = 8.88 (1H, s), 7.60 (2H, m), 7.27 (2H, m), 7.02 (1H, m), 5.40 (1H, s); ^{13}C (100 MHz, Acetone-d_6): δ = 164.4, 140.7, 129.6, 123.7, 119.7, 119.6, 48.6; IR ν_{max} (CH_2Cl_2 film)/cm^{-1} 3085, 2093 (diazo), 1631, 1600, 1548, 1442, 1369; HRMS (ESI): $C_8H_7N_3O$ requires $[M+H]^+$, calculated 162.0667, found 162.0655. Spectroscopic data matches literature [24]

2-Diazo-N-(3-methyl-1,2-oxazol-5-yl)propenamide, 2l

By general procedure A, **6a** (4.3 mmol, 1.12 g) and 5-amino-3-methylisoxazole (4.3 mmol, 422 mg), a crude material was obtained and purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the diazo acetamide **2q** as a bright orange oil (170 mg, 24%); ^1H (500 MHz, Acetone-d_6): δ = 10.17 (1H, s), 6.13 (1H, s), 5.99 (1H, s), 2.19 (3H, s). ^{13}C (125 MHz, Acetone-d_6): δ = 162.7 (rot-A), 162.6 (rot-B), 162.2 (rot-A), 162.1 (rot-B), 161.6 (rot-A/B), 88.7 (rot-A), 88.6 (rot-B), 49.3 (rot-A/B), 11.6 (rot-A/B); IR ν_{max} (CH_2Cl_2 film)/cm^{-1} 3205, 2109 (diazo), 1648, 1551, 1381, 1364, 1197, 1155; R_f 0.49 (Et_2O); HRMS (ESI): $C_6H_6N_4O_2$ requires $[M+H]^+$, calculated 189.0388, found 189.0379.

***N*-{4-[(*tert*-Butyldimethylsilyl)oxy]-3-(propan-2-yl)phenyl}-2-diazoacetamide, 2m**

By general procedure A1, **6a** (2.7 mmol, 700 mg) and aniline **S3** (500 mg, 1.9 mmol) gave a crude material which was purified using column chromatography eluting with pentane–Et_2O (1:1) to yield the *diazo acetamide* **2r** as a yellow solid (333 mg, 50%); ^1H (500 MHz, Acetone-d_6): δ = 8.72 (1H, br s, NH), 7.42 (1H, d, *J* 2.6, 2–H), 7.37 (1H, dd, *J* 8.6 and 2.6, 6–H), 6.77 (2H, d, *J* 8.6, 5–

H), 5.36 (1H, s, diazoacetamide 2–H), 3.33 (1H, hep, *J* 6.9, propan-2-yl 2–H), 1.18 (6H, d, *J* 6.9 propan-2-yl 1–H and 3–H), 1.04 (9H, s, tert-butyl–H), 0.25 (6H, s, dimethyl–H); ^{13}C (125 MHz, Acetone-d_6): δ = 164.1, 149.2, 139.8, 134.7, 119.3, 118.4, 118.3, 48.4, 27.5, 26.3, 23.3, 19.0, -3.9; R_f 0.2 (Pentane–Et_2O, 1:1); IR ν_{max} (film)/cm^{-1} 3279, 3085, 2959, 2929, 2886, 2858, 2101, 1622, 1602, 1550, 1490, 1471; HRMS (ESI) $C_{17}H_{28}N_3O_2Si$ requires $[M+H]^+$, calculated 334.1951, found 334.1949.

_N_-{4-[(*tert*-Butyldimethylsilyl)oxy]-3-(propan-2-yl)phenyl}-2-diazo-_N_-methyl-acetamide, 2n

By general procedure A1, **6a** (2.7 mmol, 700 mg) and aniline **S4** (1.8 mmol, 500 mg) gave a crude material which was purified using column chromatography eluting with pentane–Et_2O (8:2) to yield the *diazo acetamide* **2s** as a yellow solid (500 mg, 79%); ^{1}H (500 MHz, Acetone-d_6): δ = 7.15 (1H, d, *J* 2.7, 2–H), 7.00 (1H, dd, *J* 8.5 and 2.7, 6–H), 6.91 (1H, d, *J* 8.5, 5–H), 4.77 (1H, s, diazoacetamide 2–H), 3.35 (1H, hept, *J* 6.9, propan-2-yl 2–H), 3.21 (3H, s, methyl–H), 1.21 (6H, d, *J* 6.9, propan-2-yl 1–H and 3–H), 1.05 (9H, s, tert-butyl–H), 0.29 (6H, s, dimethyl–H); ^{13}C (126 MHz, Acetone-d_6): δ = 166.0, 153.0, 141.3, 137.8, 126.4, 126.4, 120.0, 47.3, 37.4, 27.7, 26.3, 23.2, 19.0, -3.9; R_f 0.4 (Pentane–Et_2O, 8:2); IR ν_{max} (film)/cm^{-1} 3280, 3085, 2959, 2930, 2859, 2101, 1622, 1602, 1549, 1491; HRMS (ESI) $C_{18}H_{30}N_3O_2Si$ requires $[M+H]^+$, calculated 348.2107, found 348.2112.

2-Diazo-2-phenyl-1-(pyrrolidin-1-yl)ethenone, 8

By general procedure A, **6b** (1.5 mmol, 500 mg) and pyrrolidine (3 mmol, 250 µL) gave a crude material which was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **8** as a yellow oil (274 mg, 63%); R_f 0.34 (Pentane–Et_2O, 1:1); ^{1}H (400 MHz, $(CD_3)_2CO$): δ = 7.97 (2H, m, Ar 2-H and 6H), 7.74 (1H, tt, *J* 7.2 and 1.2, Ar 4-H), 7.61 (2H, app t, *J* 7.2 Ar 3-H and 5-H), 3.74 (4H, m, pyr 2-H_{AB} and 5-H_{AB}), 3.61 (2H, m, pyr 3-H_{AB}), 3.38 (2H, m, pyr 4-H_{AB}); ^{13}C (101 MHz, $(CD_3)_2CO$): δ = 165.2, 134.7, 129.4, 129.1, 128.6, 127.3, 66.4, 66.2, 46.0, 41.2; IR ν_{max} (neat)/cm^{-1} 2925, 2101, 1646.

2-[4-Cyano-3-(trifluoromethyl)phenyl]-2-diazo-_N,N_-dipropylacetamide, 9a

By general procedure B2 (1 mmol scale), **S11** (1 mmol, 169 mg) and 4-iodo-2-(trifluoromethyl)benzonitrile (1 mmol, 297 mg) gave a crude material which was purified using column chromatography eluting with CH_2Cl_2–Et_2O (19:1) to yield the *diazo acetamide* **9a** as a red solid (277 mg, 82%); R_f 0.52 (Pentane–Et_2O, 1:1); ^{1}H (400 MHz, $(CD_3)_2CO$): δ = 8.00 (1H, d, *J* 8.4, Ar 5-H), 7.86 (1H, d, *J* 1.9, Ar 2-H), 7.68 (1H, dd, *J* 8.4 and 2.0, Ar 6-H), 3.43-3.35 (4h, m, propyl 1-H), 1.65 (4H, sx, *J* 7.4, propyl 2-H), 0.89 (6H, t, *J* 7.4, propyl 3-H); ^{13}C (101 MHz, $(CD_3)_2CO$): 162.3, 136.2, 135.2, 132.2, 126.2, 124.1, 121.0, 115.5, 104.1, 48.9, 20.8, 10.5 (1 signal missing); IR ν_{max} (neat)/cm^{-1} 2960, 2937, 2878, 2228, 2068, 1632 and 1434; HRMS (ESI): $C_{16}H_{18}F_3N_4O$ requires $[M+H]^+$, calculated 339.1433, found 339.1423

4-[1-Diazo-2-oxo-2-(pyrrolidin-1-yl)ethyl]-2-(trifluoromethyl)benzonitrile, 9b

By general procedure B2 (0.5 mmol scale), **2f** (0.5 mmol, 70mg) and 4-iodo-2-(trifluoromethyl)benzonitrile (0.5 mmol, 149 mg) gave a crude material which was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **9b** as a red solid (119 mg, 77%); R_f 0.33 (Et_2O); ^{1}H (400 MHz, $(CD_3)_2CO$): 8.09 (1H, d, *J* 2.0, Ar 3-H), 7.99 (1H, d, *J* 8.4, Ar 6-H), 7.77 (1H, dd, *J* 8.4 2.0, Ar 5-H), 3.52 (4H, m, 2-H_{AB}, 5-H_{AB}), 2.00 – 1.81 (4H, m, 3-H_{AB}, 4-H_{AB}); ^{13}C (101 MHz, $(CD_3)_2CO$): δ = 161.5, 136.9, 135.9, 132.5, 127.2, 125.5, 122.3, 121.9, 116.5, 105.0, 48.3, 25.9 (1 signal missing); IR ν_{max} (neat)/cm^{-1} 2899, 2848, 2193, 2045, 1675 and 1390; HRMS found MNa$^+$: 331.0776 ($C_{14}H_{11}F_3N_4ONa$ *requires MNa*, 331.0783)

2-Diazo-2-(4-nitrophenyl)-1-(pyrrolidin-1-yl)ethenone, 9c

By general procedure B1 (1.53 mmol scale), **2f** (2 mmol, 280 mg) and 4-iodo-1-nitrobenzene (1.53 mmol, 310 mg) gave a crude material which was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **9c** as a dark orange solid (226 mg, 57%); ^{1}H (501 MHz, DMSO-d_6): δ = 7.77-7.74 (2 H, app m, *J* 9.1 and 2.0, phenyl 3–H and 5–H), 7.14-7.11 (2 H, app m, *J* 9.1 and 2.0, phenyl 2–H and 6–H), 2.97 (4 H, app m, pyrrolidinyl 2–H_{ab} and 5–H_{ab}), 1.42 (4 H, m, pyrrolidinyl 3–H_{ab} and 4–H_{ab}); ^{13}C (126 MHz, DMSO-d_6): δ = 160.93, 144.40, 136.97, 131.52, 130.73, 64.05, 47.88, 25.31; R_f 0.6 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (neat)/cm^{-1} 2062, 1625, 1525, 1391, 1346, 1235, 1170, 826; HRMS Found MNa+:283.0800 ($C_{12}H_{12}N_4NaO_3$ requires MNa, 283.0807).

4-[1-Diazo-2-oxo-2-(pyrrolidin-1-yl)ethyl]-3-methylbenzonitrile, 9d

By general procedure B1 (1 mmol scale), **2f** (1.3 mmol, 180 mg) and 4-bromo-3-methylbenzonitrile (1 mmol, 196 mg) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **9d** as a pale yellow solid (119 mg, 47%); ^{1}H (501 MHz, Acetone-d_6): δ = 7.78 (1 H, d, *J* 8, 5–H), 7.66 (1 H, app s, 2–H), 7.63 (1 H, app d, *J* 8, 5–H), 3.40 (4 H, m, pyrrolidinyl 2–H_{ab} and 5–H_{ab}), 2.48 (3 H, s, 3-methyl–H_3), 1.84 (4 H, m, pyrrolidinyl 3–H_{ab} and 4–H_{ab}); ^{13}C (126 MHz, Acetone-d_6): δ = 192.76, 164.07, 141.16, 136.39, 135.29, 132.13, 129.67, 117.63, 115.90, 46.41, 45.17, 25.67, 23.63, 19.82; R_f 0.46 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (neat)/cm^{-1} 2231, 1685, 1637, 1444, 1220, 1012, 848, 708; HRMS (ESI) HRMS Found MH-N_2+:227.1177 ($C_{14}H_{15}N_2O$ requires MH-N_2, 227.1184).

2-Diazo-2-(4-methyl-3-nitrophenyl)-1-(pyrrolidin-1-yl)ethenone, 9e

By general procedure B1 (0.83 mmol scale), **2f** (1.1 mmol, 153 mg) and 4-iodo-1-methyl-2-nitrobenzene (0.83 mmol, 218 mg) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **9e** as an orange solid (118 mg, 48%); ^{1}H (501 MHz, Acetone-d_6): δ = 7.94 (1 H, d, *J* 2.0, 2–H), 7.37 (1 H, dd, *J* 8.2 and 2.0, 5–H), 7.3 (1 H, d, *J* 8.2, 56H), 3.33 (4 H, m, pyrrolidinyl 2–H_{ab} and 5–H_{ab}), 2.36 (3 H, s, 3-methyl–H_3), 1.79 (4 H, m, pyrrolidinyl 3–H_{ab} and 4–H_{ab}); ^{13}C (126 MHz, Acetone-d_6): δ = 161.77, 149.79 133.00, 129.27 127.91, 119.87, 47.47, 25.10, 18.74; R_f 0.55 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (neat)/cm^{-1} 2066, 1627, 1590, 1510, 1393, 1337, 1111, 850, 751; HRMS Found MNa+:297.0960 ($C_{13}H_{14}N_4NaO_3$ requires MH, 297.0963).

2-Diazo-2-(3,4-dichlorophenyl)-1-(pyrrolidin-1-yl)ethenone, 9f

By general procedure B1 (1 mmol scale), **2f** (1.3 mmol, 180 mg) and 1,2-dichloro-4-iodobenzene (1 mmol, 273 mg) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazo acetamide* **9f** as an orange oil (96 mg, 34%); ^{1}H (501 MHz, Acetone-d_6): δ = 7.70 (1

H, app d, *J* 2.20, 5–H), 7.56-7.53 (1 H, app m, 2–H), 7.31 (1 H, m, 6–H), 3.46 (4 H, app m, pyrrolidinyl 2–H_{ab} and 5–H_{ab}), 1.93 (4 H, m, pyrrolidinyl 3–H_{ab} and 4–H_{ab}); ^{13}C (126 MHz, Acetone-d_6): δ = 161.65, 132.16, 130.57, 129.35, 127.76, 125.84, 123.70, 54.08, 47.43, 25.06; R_f 0.51 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (film)/cm^{-1} 2062, 1626, 1474, 1388, 1338, 1135, 1027, 735; HRMS Found MNa+:306.0170 ($C_{12}H_{11}Cl_2N_3NaO$ requires MNa, 306.0177).

_N_-[(4-Chlorophenyl)methyl]-2-diazo-_N_-methyl-2-[4-(trifluoromethyl)phenyl]acetamide, 9g

By general procedure B1 (3 mmol scale), **S8** (3.9 mmol, 872 mg) and 4-trifluoromethyl-iodobenzene (3 mmol, 440 µl) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield *aryl diazo acetamide* **9g** as a bright orange oil (535 mg, 1.46 mmol, 49%); R_f 0.5 (CH_2Cl_2–Et_2O, 9:1); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.54 (2H, d, *J* = 8.4 Hz, Ar(F)-3H), 7.29-7.25 (4H, m, Ar(F)-2H and Ar(Cl)-3H), 7.16 (2H, d, *J* = 8.5 Hz, Ar(Cl)-2H), 4.51 (2H, s, ArC*H*$_2$), 2.80 (3H, s, N-C*H*$_3$); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 164.5, 134.9, 133.8, 131.9, 129.4, 129.1, 126.1 (q, $J^3_{F\text{-}C}$ = 4 Hz), 123.9, 62.7 (verified through HMBC spectrum), 52.1, 36.1 (2 signals missing); IR: ν_{max}/cm^{-1} (film) 3096, 2107, 1632, 1208; HRMS: $C_{17}H_{13}ClF_3N_3ONa$ (*MNa*) Requires: 390.0591, Found: 390.0586.

2-Diazo-_N_,_N_-diethyl-2-[4-(trifluoromethyl)phenyl]acetamide, 9h

By general procedure B1 (2 mmol scale), **S9** (2.6 mmol, 366 mg) and 4-trifluoromethyl-iodobenzene (2 mmol, 294 µl) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *aryl diazo acetamide* **9h** as a bright orange oil (264 mg, 0.97 mmol, 47%); R_f 0.45 (CH_2Cl_2–Et_2O, 9:1); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.52 (2H, d, *J* = 8.4 Hz, Ar-3H), 7.24 (2H, d, *J* = 8.4 Hz, Ar-2H), 3.34 (4H, q, *J* = 7.1 Hz, Et-1H), 1.13 (6H, t, *J* = 7.1 Hz, Et-2H); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 163.6, 132.4, 127.6 (q, $J^2_{F\text{-}C}$ = 29 Hz), 125.9 (q, $J^3_{F\text{-}C}$ = 4 Hz), 125.5 (q, $J^1_{F\text{-}C}$ = 277 Hz), 61.5, 41.9, 13.2 (2 signals missing); IR ν_{max}/cm^{-1} (film) 3083, 2111, 1644, 1204; HRMS: $C_{13}H_{15}F_3NO$ (*MH-N*$_2$) Requires: 258.1100, Found: 258.1102.

2-Diazo-_N_,_N_-diethyl-2-(4-nitrophenyl)acetamide, 9i

By general procedure B1 (2 mmol scale), **S9** (2.6 mmol, 366 mg) and 4-nitro-iodobenzene (2 mmol, 498 mg) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *aryl diazo acetamide* **9i** as a bright orange amorphous solid (277 mg, 1.1 mmol, 53%); R_f 0.45 (CH_2Cl_2–Et_2O, 9:1); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.13 (2H, d, *J* = 9.1 Hz, Ar-3H), 7. 27 (2H, d, *J* = 9.1 Hz, Ar-2H), 3.36 (4H, q, *J* = 7.1 Hz, Et-1H), 1.16 (6H, t, *J* = 7.1 Hz, Et-2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ = 162.7, 144.8, 136.3, 124.4, 123.3, 62.2 (verified through HMBC spectrum), 42.0, 13.2; IR ν_{max}/cm^{-1} (film) 3029, 2119, 1659, 1503; HRMS: $C_{12}H_{15}N_2O_3$ (*MH-N*$_2$) Requires: 235.1077, Found: 235.1074.

_N_-[2-(4-Chlorophenyl)ethyl]-2-diazo-_N_-methyl-2-[4-(trifluoromethyl)phenyl]acetamide, 9j

By general procedure B1 (4 mmol scale), **S10** (5.2 mmol, 1.23g) and 4-trifluoromethyl-iodobenzene (4 mmol, 589 µL) gave a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *aryl diazo acetamide* **9j** as a bright orange oil (769 mg, 2.01 mmol, 50%); R_f 0.52 (CH_2Cl_2–Et_2O, 9:1); ^{1}H NMR (400 Hz, $CDCl_3$); δ = 7.49 (2H, d, *J* = 8.3 Hz, Ar(F)-3H), 7.20 (2H, d, *J* = 8.3 Hz, Ar(F)-2H), 7.09 (2H, 2H, d, *J* = 8.1 Hz, Ar(Cl)-3H), 7.06 (2H, d, *J* = 8.1 Hz, Ar(Cl)-2H), 3.57 (2H, t, J = 7.3 Hz, ArCH$_2$C*H*$_2$), 2.86-2.81 (5H, m, ArC*H*$_2$CH$_2$, and N-C*H*$_3$); ^{13}C NMR (125 Hz, $CDCl_3$) δ = 164.4, 136.7, 132.6, 131.9, 130.1, 128.8, 127.6 (q, $J^2_{F\text{-}C}$ = 29 Hz), 125.9 (q, $J^3_{F\text{-}C}$ = 3 Hz), 123.8, 62.4 (verified through HMBC spectrum), 50.7, 36.6, 33.1; IR ν_{max}/cm^{-1} (film) 3087, 2113, 1652, 1199; HRMS: $C_{18}H_{16}ClF_3N_3O$ (*MH*) Requires: 382.0929; Found: 382.0924.

***tert*-Butyl (1R,5S)-8-{[4-cyano-3-(trifluoromethyl)phenyl](diazo)acetyl}-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, 10a**

By telescoping general procedures A and B2 (0.25 mmol scale), a crude material was obtained and purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazoacetamide* **10a** as a yellow oil (49 mg, 44%); R_f 0.10 (Et_2O); ^{1}H (400 MHz, $(CD_3)_2CO$): δ = 7.89 (2H, m, Ar 5-H, 2-H), 7.67 (1H, m, Ar 6-H), 4.29 (2H, app s, 3-H, 6-H), 3.75 (2H, m, 2-H_A, 7-H_A), 2.96 (2H, m, 2-H_B, 7-H_B), 1.81 (2H, m, 4-H_A, 5-H_A),1.63 ((2H, m, 4-H_B, 5-H_B), 1H), 1.32 (3H, s, tert-butyl); ^{13}C (101 MHz, $(CD_3)_2CO$): δ = 163.3, 156.0, 136.4, 136.2, 127.5, 122.3, 116.4, 105.4, 80.1, 55.4, 27.3; HRMS found MNa$^+$: 472.1564 ($C_{21}H_{22}F_3N_5O_3Na$ *requires MNa*, 472.1572).

5-Diazo-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione, 12a

By general procedure C1, to 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (6.4 mmol, 1.00 g) and *p*-ABSA (9.6 mmol, 2.30 g) in MeCN (0.12 M, 54 mL) was added NEt_3 (1.10 mL, 7.68 mmol) dropwise at -10 °C and allowed to react at room temperature for 30 min. The crude material was purified by column chromatography eluting with EtOAc–petrol (1:1) to give the *diazo compound* as a pale yellow amorphous solid (1.025 g, 88%); ^{1}H (501 MHz, methylene chloride-d_2): δ = 3.27 (6 H, s, dimethyl); ^{13}C (126 MHz, methylene chloride-d_2): δ = 158.53, 150.88, 71.93, 28.60; R_f 0.55 (EtOAc–petrol, 1:1); IR ν_{max} (neat)/cm^{-1} 2155, 1710, 1638, 1468, 1415, 1372, 1291, 1245, 1066; HRMS (ESI) Molecular ion not found. Spectroscopic data matches literature.[25]

3-Diazo-2,4-piperidinedione, 12b

By general procedure C1, to 2,4-piperidinedione (4.42 mmol, 500 mg) and *p*-ABSA (6.63 mmol,1.59 g) in MeCN (0.12 M, 37 mL) was added NEt_3 (0.73 mL, 5.30 mmol) dropwise at -10 °C and allowed to react at room temperature for 30 min. The crude material was purified by column chromatography eluting with CH_2Cl_2–MeOH (9:1). The product was further purified by column chromatography eluting with Et_2O to give the *diazo compound* as a colourless amorphous solid (204 mg, 33%); ^{1}H (501 MHz, methylene chloride-d_2): δ = 6.96 (1H, s, NH), 3.45 (2H, td, *J* 6.5, 2.8, 6–H), 2.60 (2H, t, *J* 6.5, 5–H); ^{13}C (126 MHz, methylene chloride-d_2): δ = 188.56, 163.72, 75.41, 37.36, 36.68; R_f 0.08 (Et_2O); IR ν_{max} (film)/cm^{-1} 3183, 3045, 2905, 2150, 1650, 1461, 1416, 1347, 1291, 1039; HRMS (ESI) Molecular ion not found. Spectroscopic data matches literature.[26]

2-Diazoindan-1,3-dione, 12c

By general procedure C1, to 1,3-indandione (3.4 mmol, 500 mg) and *p*-ABSA (5.1 mmol, 1.22 g) in MeCN (0.12 M, 30 mL) was added NEt_3 (0.57 mL, 4.08 mmol) dropwise at -10 °C and allowed to react at room temperature for 1 h. The crude material was purified by column chromatography eluting with CH_2Cl_2 to give the *diazo compound* as a yellow amorphous solid (446 mg, 76%); ^{1}H (501 MHz, methylene chloride-d_2): δ = 7.84-7.79 (2 H, m, 4– and 7–H), 7.78-7.74 (2 H, m, 5– and 6–H); ^{13}C

(126 MHz, Methylene Chloride-d_2): δ = 182.39, 137.57, 135.17, 122.88, 70.39; R_f 0.40 (CH_2Cl_2); IR ν_{max} (neat)/cm^{-1} 2119, 1688, 1594, 1350, 1329, 1265, 1188, 738, 709; HRMS (ESI) Molecular ion not found. Spectroscopic data matches literature.[27]

5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione, 12d

By general procedure C1, to 2,2-dimethyl-1,3-dioxane-4,6-dione (3.5 mmol, 500 mg) and *p*-ABSA (5.25 mmol, 1.26 g) in MeCN (0.12 M, 30 mL) was added NEt_3 (4.20 mmol, 0.58 mL) dropwise at -10 °C and allowed to react at room temperature for 30 min. The crude material was purified by column chromatography eluting with CH_2Cl_2 to give the *diazo compound* as a colourless amorphous solid (541 mg, 91%); ^{1}H (501 MHz, methylene chloride-d_2): δ = 1.76 (6H, s, dimethyl); ^{13}C (126 MHz, methylene chloride-d_2): δ = 158.65, 107.40, 64.39, 26.95; R_f 0.38 (CH_2Cl_2); IR ν_{max} (neat)/cm^{-1} 2175, 1706, 1308, 1296, 1191, 1165, 1026, 977, 905; HRMS (ESI). Molecular ion not found. Spectroscopic data matches literature.[28]

***N*-(3-Chloro-4-methoxyphenyl)-2-diazo-N-methyl-3-oxobutanamide, 13a**

By general procedure C2, 3-chloro-4-methoxy-N-methylaniline (3.5 mmol, 600 mg) in toluene (1.4 M, 2.5 mL) and 2,2,6-trimethyl-1,3-dioxin-4-one (3.85 mmol, 510 µL) were reacted under µW irradiation at 110 °C for 1.5 h. The crude material was purified by column chromatography eluting with CH_2Cl_2–MeOH (98:2) to give the butanamide (840 mg, 94%). By general procedure C3, to the butanamide (840 mg, 3.28 mmol) and *p*-ABSA (1.20 g, 4.92 mmol) in MeCN (0.12 M, 28 mL) was added NEt_3 (0.55 mL, 3.94 mmol) to give a crude material which was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to give the *diazo compound* as a light yellow, low melting solid (412 mg, 45%); ^{1}H (501 MHz, methylene chloride-d_2): δ = 7.27 (1H, d, *J* 2.6, aryl 2–H), 7.12 (1H, dd, *J* 8.7, 2.6, aryl 6–H), 6.97 (1H, d, *J* 8.7, aryl 5–H), 3.91 (3H, s, methoxy), 3.29 (3H, s, N-methyl), 2.44 (3H, s, methyl); ^{13}C (126 MHz, methylene chloride-d_2): δ = 191.62, 161.06, 155.10, 136.47, 128.71, 126.59, 123.71, 113.19, 73.95, 56.81, 38.74, 28.57; R_f 0.43 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (film)/cm^{-1} 3360, 2110, 1642, 1499, 1361, 1265, 1247, 1062, 1020; HRMS (ESI) $C_{12}H_{12}ClN_3O_3$ requires $[M+Na]^+$, calculated 304.0460, found 304.0456.

***N*-(4-Chlorophenyl)-2-diazo-*N*-methyl-3-oxobutanamide, 13b**

By general procedure C2, 4-Chloro-*N*-methyl aniline (8.3 mmol, 1.00 mL) in toluene (8 mL) and 2,2,6-trimethyl-1,3-dioxin-4-on (12.5 mmol, 1.66 mL) were reacted under µW irradiation at 110 ^{o}C for 30 min. The crude material, *p*-ABSA (9.1 mmol, 2.20 g) and triethylamine (1.30 mL, 9.1 mmol) were then added and the reaction allowed to warm to room temperature over 16 hours. A white precipitate formed, which was removed by filtration, and the solvent then removed under reduced pressure to give a dark red oil which was purified by column chromatography eluting CH_2Cl_2, then CH_2Cl_2–Et_2O (9:1) to give the *diazo compound* **13b** as a yellow oil that solidified on standing (1.34 g, 64%); ^{1}H (400 MHz, $CDCl_3$): δ = 7.39 (2H, d, *J* 8.7), 7.14 (2H, d, *J* 8.7), 3.34 (3H, s), 2.46 (3H, s); ^{13}C (100 MHz, $CDCl_3$): δ = 191.4, 161.1, 157.1, 141.7, 133.9, 130.6, 127.5, 38.6, 28.5; IR ν_{max} (CH_2Cl_2 film)/cm^{-1} 2184 (diazo), 1636, 1590, 1487, 1356; R_f 0.10 (CH_2Cl_2); HRMS (ESI): $C_{11}H_{10}ClN_3O_2$ requires $[M+Na]^+$, calculated 274.0359, found 274.0350.

1-(6-Chloro-3,4-dihydro-2H-quinolin-1-yl)-2-diazobutane-1,3-dione, 13c

By general procedure C2, to 6-chloro-1,2,3,4-tetrahydroquinoline (3.0 mmol, 500 mg) in toluene (1 M, 3.00 mL) was added 2,2,6-trimethyl-1,3-dioxin-4-one (3.3 mmol, 440 µL) and the solution was reacted under µW irradiation at 110 °C for 1.5 hr. The crude product was purified by silica column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to give the butanamide (744 mg, 99%). By general procedure C3, to the butanamide (0.70 g, 2.78 mmol) and *p*-ABSA (1.00 g, 4.17 mmol) in MeCN (0.12 M, 23 mL) was added NEt_3 (0.46 mL, 3.34 mmol). After 4h, the crude material was purified by column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to give the *diazo compound* as a light yellow, low melting solid (439 mg, 57%); ^{1}H (501 MHz, methanol-d_4): δ = 7.32 (1H, d, *J* 8.6, quinolinyl 5–H), 7.25 (1H, d, *J* 2.5, quinolinyl 8–H), 7.17 (1 H, dd, *J* 8.6, 2.5, quinolinyl 7–H), 3.75 (2H, t, *J* 6.5, quinolinyl 2–H), 2.74 (2H, t, *J* 6.5, quinolinyl 4–H), 2.32 (3H, s, methyl), 1.98 (2H, p, *J* 6.5, quinolinyl 3–H); ^{13}C (126 MHz, methanol-d_4): δ = 191.12, 162.46, 138.42, 135.83, 131.68, 129.70, 127.87, 124.85, 77.41, 45.90, 27.56, 27.44, 24.76; R_f 0.43 (CH_2Cl_2–Et_2O, 9:1); IR ν_{max} (film)/cm^{-1} 2950, 2891, 2107, 1632, 1484, 1345, 1255, 1197, 1170, 1090, 946; HRMS (ESI) $C_{13}H_{12}ClN_3O_2$ requires $[M+Na]^+$, calculated 300.0511, found 300.0508.

2-Diazo-1-[(2*R*,6*S*)-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridin-1-yl]butane-1,3-dione, 13d

By general procedure C2, to (2*R*,6*S*)-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (996 mg, 5 mmol) the diazo transfer was performed for 24 h followed by purification with column chromatography, eluting with CH_2Cl_2 to give the *diazo compound* **13d** as a yellow oil (0.339 g, 22%); ^{1}H (501 MHz, Acetone-d_6): δ = 7.33 (2H, d, *J* 7.9, phenyl 2–H and 6–H), 7.27 (2H, app t, *J* 7.9, phenyl 3–H and 5–H), 7.17 (1H, app t, *J* 7.9, phenyl 4–H), 5.87 (1H, ddt, *J* 17.1, 10.1 and 7.4, allyl 2–H), 5.76 (1H, dd, *J* 2.3 and 10.0, pyridinyl 5–H), 5.69 (1H, dt, *J* 10.0 and 3.0, pyridinyl 4–H), 5.21 (1H, d, *J* 2.3, pyridinyl 6-–H), 5.14 (1H, d, *J* 17.1, allyl 3–H_{trans}), 5.09 (1H, dd, *J* 10.1 and 2.0, allyl 3–H_{cis}), 4.29 (1H, m, pyridinyl 2–H), 2.83 (1H, m, allyl 1–H_a), 2.62 (1H, m, pyridinyl 3–H_a), 2.35 (1H, m, pyridinyl 3–H_b), 2.23 (1H, m, allyl 1–H_b), 2.21 (3H, s, butane 4–H); ^{13}C (75 MHz, Acetone-d_6): δ = 189.0, 164.0, 144.0, 136.4, 130.2, 129.2, 127.5, 127.5, 121.4, 118.5, 76.1, 58.3, 54.8, 38.8, 29.4, 27.3; R_f 0.14 (CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3033, 2114, 1697, 1655, 1611, 1493, 1449; HRMS (ESI) $C_{18}H_{19}N_3O_2Na$ requires $[M+Na]^+$, calculated 332.1370, found 332.1369.

2-Diazo-1-{3-oxo-2-azabicyclo[2.2.1]hept-5-en-2-yl}butane-1,3-dione, 13e

By general procedure C2, to 2-azabicyclo[2,2,1]hept-5-en-3-one (500 mg, 4.6 mmol) the diazo transfer was performed for 24 h, followed by purification with column chromatography, eluting with Petrol–EtOAc (7:3), to give the *diazo compound* **13e** as a yellow oil (0.29 g, 29%); ^{1}H (400 MHz, $CDCl_3$): δ = 6.91 (1H, dd, *J* 5.2 and 2.3, 5–H), 6.48 (1H, dd, *J* 5.2 and 3.3, 6–H), 4.79 (1H, m, 4–H), 3.35 (1H, m, 1–H), 2.30 (3H, s, methyl–H), 2.21 (1H, dt, *J* 8.8 and 1.4, 7–H_a), 2.11 (1H, dt, *J* 8.8 and 1.3, 7–H_b); ^{13}C (400 MHz, $CDCl_3$): δ = 189.8, 175.6, 160.3, 140.6, 136.1, 62.2, 53.7, 53.0, 28.4; R_f 0.27 (Petrol–EtOAc, 7:3); IR ν_{max} (film)/cm^{-1} 2955, 2139, 1745, 1651, 1302; HRMS (ESI) $C_{10}H_9N_3NaO_3$ requires $[M+Na]^+$, calculated 242.0538, found 242.0535.

2-Diazo-1-(4-isopropyl-2-oxopyrrolidin-1-yl)butane-1,3-dione, 13f

By general procedure C2, with 4-isopropylpyrrolidin-2-one (500 mg, 3.93 mmol) the diazo transfer was performed for 24 h followed by purification with column chromatography, eluting with CH_2Cl_2–MeOH (99:1) to give the *diazo compound* **13f** as a yellow amorphous solid (0.376 g, 40%); ^{1}H (400 MHz, Acetone-d_6): δ = 3.89 (1H, dd, *J* 10.8 and 7.8, pyrrolidinyl 5–H_a), 3.51 (1H, dd, *J* 10.8 and 9.2, pyrrolidinyl 5–H_b), 2.64 (1H, dd, *J* 17.4 and 8.3, pyrrolidinyl 3–H_a), 2.42 (1H, dd, *J* 17.4 and 8.3, pyrrolidinyl 3–H_b), 2.39 (3H, s, butane 4–H), 2.14 (1H, td, *J* 17.4 and 8.3, pyrrolidinyl 4–H), 1.68 (1H, m, isopropyl–H), 0.96 (6H, d, *J* 6.7, isopropyl–H); ^{13}C (101 MHz, Acetone-d_6): δ = 190.2, 174.5, 160.6, 79.2, 51.0, 38.8, 38.1, 32.6, 28.6, 20.7, 20.3; R_f 0.24 (CH_2Cl_2–MeOH, 99:1); IR ν_{max} (film)/cm^{-1} 2962, 2133, 1732, 1650, 1316, 1204; HRMS (ESI) $C_{11}H_{15}NO_3Na$ requires [M-N_2+Na]$^+$, calculated 232.0944, found 232.0942.

2-Diazo-1-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]butane-1,3-dione, 13g

By general procedure C2, using (4*S*)-4-phenyl-1,3-oxazolidin-2-one (1.5 g, 9.2 mmol) with the diazo transfer performed for 24 h followed by purification with column chromatography, eluting with CH_2Cl_2 to give the *diazo compound* **13g** as a white amorphous solid (1.280 g, 53%); ^{1}H (400 MHz, methylene chloride-d_2): δ = 7.41 (5H, m, phenyl 2–H, 3–H, 4–H, 5–H and 6-H), 5.59 (1H, t, *J* 8.8, oxazolidinyl 4–H), 4.77 (1H, app t, *J* 8.8, oxazolidinyl 5–H_a), 4.25 (1H, app t, *J* 8.8, oxazolidinyl 5–H_b), 2.37 (3H, s, butane 4–H); ^{13}C (101 MHz, methylene chloride-d_2): δ = 189.7, 160.0, 153.6, 137.3, 129.6, 129.5, 127.1, 80.0, 70.8, 59.2, 28.8; R_f 0.17 (CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3058, 2136, 1775, 1656, 1308, 1207; HRMS (ESI) $C_{13}H_{11}NO_4Na$ requires [M-N_2+Na]$^+$, calculated 268.0580, found 268.0577.

2-Diazo-2-(3,4-dichlorophenyl)-*N*-methyl-*N*-phenylacetamide, 9k

By general procedure C3 (1 mmol scale), 2-(3,4-dimethylphenyl)-N-methyl-N-phenylacetamide (293 mg, 1 mmol) and *p*-ABSA (264 mg, 1.1mmol) gave a crude material and was purified using column chromatography eluting with CH_2Cl_2–Et_2O (9:1) to yield the *diazoacetamide* **9k** as an orange oil (252 mg, 79%); R_f 0.67 (Pentane–Et_2O, 1:1); ^{1}H (400 MHz, $(CD_3)_2CO$): δ = 7.63 (1H, d, *J* 2.3, dichloroPhe 2-H), 7.48 (2H, d, *J* 8.5, dichloroPhe 5-H), 7.42 (2H, m, NPhe 3-H, 5-H), 7.34 (2H, m, NPhe 2-H, 6-H), 7.28 (1H, m, NPhe 4-H), 7.18 (1H, dd, *J* 8.5, 2.3, dichloroPhe 6-H), 3.38 (3H, s, NMe); ^{13}C (101 MHz, $(CD_3)_2CO$): δ = 164.2, 145.0, 132.9, 131.4, 130.8, 130.1, 128.9, 127.7, 127.0, 126.6, 124.6, 112.7, 38.7; HRMS (ESI): $C_{15}H_{12}Cl_2NO$ requires [M-N_2+H]$^+$, calculated 292.0296, found 292.0277.

***N*,2-bis(4-chlorophenyl)-2-diazo-*N*-methylacetamide, 9l**

By general procedure C3, *N*,2-bis(4-chlorophenyl)-*N*-methylacetamide (300 mg, 1.0 mmol) and *p*-ABSA (269 mg, 1.1 mmol) gave a viscous orange oil that was purified by flash column chromatography eluting with pentane–Et_2O (9:1) to give the *diazo compound* **9l** as an orange oil (114 mg, 35%); ^{1}H (400 MHz, Acetone-d_6): δ = 7.42-7.39 (2H, m), 7.36-7.30 (6H, m), 3.36 (3H, s); ^{13}C (101 MHz, $(CD_3)CO$): δ = 164.9, 144.2, 132.7, 131.7, 130.8, 130.0, 129.7, 128.3, 127.7, 127.2, 38.7; IR ν_{max} (CH_2Cl_2 film/cm^{-1} 2066 (diazo), 1635, 1490, 1313; R_f 0.14 (1:1 Pentane/Et_2O). HRMS (ESI): $C_{15}H_{11}Cl_2N_3O$ requires [M+Na]$^+$, calculated 342.0177, found 342.0165.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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