This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Chemical Science

ARTICLE

Flow Chemistry as a Discovery Tool to Access sp²-sp³ Cross-Coupling Reactions via Diazo Compounds

Duc N. Tran,[a] Claudio Battilocchio,[a] Shing-Bong Lou,[a] Joel M. Hawkins,[b] and Steven V. Ley*[a]

The work takes advantage of an important feature of flow chemistry, whereby the generation of a transient species (or reactive intermediate) can be followed by a transfer step into another chemical environment, before the intermediate is reacted with a coupling partner. This concept is successfully applied to achieve a room temperature sp²-sp³ cross coupling of boronic acids with diazo compounds, these latter species being generated from hydrazones under flow conditions using MnO_2 as the oxidant.

Introduction

Chemical processes define our modern world in terms of providing society's functional materials.[1] Many of these processes involve complex reaction pathways and proceed *via* transient reactive intermediates. The lifetime of these reactive species can vary enormously and their selectivity can often be difficult to exploit. Their high level of reactivity, when generated in batch mode, can be problematic because of incompatibilities with their chemical environment or functional groups, or because of associated exothermic properties. A case in point relates to diazo compounds which are valuable reactive intermediates.[2] For example, isolated stabilised diazo compounds, bearing one or more electron withdrawing groups, have been extensively investigated in a wide range of applications such as dipolar cycloadditions,[3] carbonyl homologation[4] and cyclopropanation.[5] However, their unstabilised alkyl and aryl diazo counterparts are much more difficult to harness.[2,6] Their chemical preparation is limited due to the often tedious, corrosive or toxic synthesis protocols.[6a,7] In-situ generation of diazo compounds therefore represents an interesting opportunity for synthesis,[8] although any new procedure must be compatible with both the generation of the diazo compound and with its subsequent chemical transformation.

Manganese dioxide (MnO_2) has been used previously in batch mode to generate diazo compounds from hydrazones, although with low efficiency and with very specific substrates.[9] Following on from the advantages that accrue when using MnO_2 under continuous flow reactions,[10] we believed that we could devise a system capable of delivering reactive *unstable* diazo compounds on demand. Also, with the aim of better exploiting the potential of the flow chemistry,[11,12] we anticipated that these flow-generated transient species could be rapidly transferred into another chemical environment, in order to react the aforementioned species with a suitable partner,

hence avoiding interference by spent reagents (Scheme 1). This generation/translocation/reaction sequence should immediately provide access to new chemical space for the discovery of new reactions for these reactive intermediates.
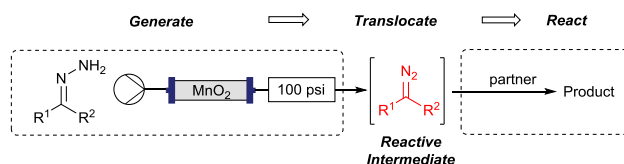

Scheme 1. Flowing scheme for the generation, translocation and reaction of the diazo species.

Metal free sp²-sp³ cross-coupling reactions have recently become a new focus of the chemical community.[13] In 2009, Barluenga et al. reported an efficient coupling between tosylhydrazones and boronic acids.[13a] Further studies with saturated heterocyclic sulfonylhydrazones by Nakagawa,[13b] Kirschning,[13c] and ourselves,[13d,e] demonstrated a wider scope for the reaction (Scheme 2). Recently, Wang and co-workers reported an efficient synthesis of α-aryl esters and nitriles via a diazotization method for the generation of *stabilised* diazo compounds.[13f] However, the relatively harsh reaction conditions (up to 110 °C), large amount of inorganic additives (bases, $NaNO_2$, NH_4Cl) and low atom economy represent potential drawbacks of these transformations. We envisaged that we could access new reactivities of *unstabilised* diazo compounds, in particular their coupling with boronic acids at room temperature.

**Barluenga, Nakagawa, Kirschning and our work [13a-d]**

Wang's work [13f]

(EWG = CO$_2$R, CN)
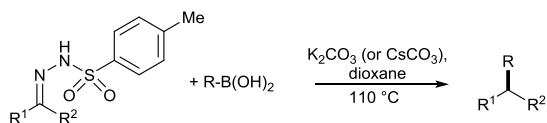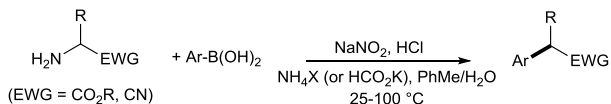
This work
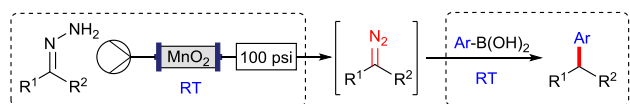
Scheme 2. Selected metal-free sp^2-sp^3 cross-coupling reactions.

Results and discussion

Generation of diazo compound

Initial investigations focused on 4-bromophenyl hydrazone (**1a**) as model substrate for the generation of the diazo compound **2a**. To evaluate the generation of the transient diazo species, the material processed was quenched with acetic acid to yield the corresponding acetic acid ester **3a** (Scheme 3).[6] Amorphous MnO$_2$ packed into the flow cartridge gave very poor conversion to **2a** with mainly starting material being recovered. By contrast, a column packed with *activated* MnO$_2$ gave full conversion to various products but with aldehyde **4a** being the main product observed. This result was also consistent with batch studies where aldehyde or azine by-products were generally observed at ca. 30% yield, even under carefully controlled reaction conditions.[9b,c,f] However, conditioning of the packed column with a small amount of sacrificial hydrazone[14] effectively reduced the formation of aldehyde and increased the production of diazo compound **2a** as determined *via* the formation of ester **3a**. Furthermore, addition of a base (Hünig's base, 2 equiv) to the feedstock solution provided a reliable system with greatly reduced amounts of by-products generated.[15]
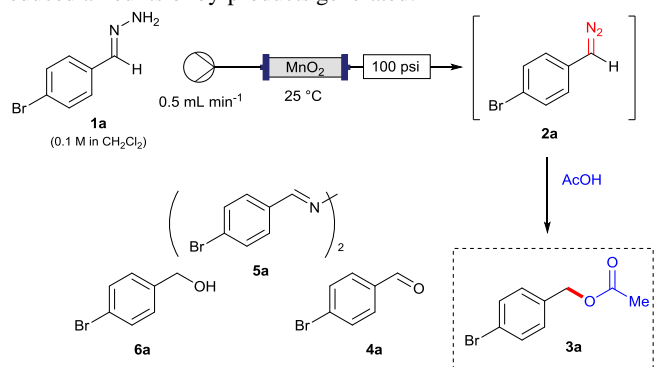

Scheme 3. Flow generation and quenching of of 1-bromo-4-(diazomethyl)benzene.

Under the optimised conditions, a 0.1 M solution of hydrazone **1** was passed through a conditioned MnO$_2$ column (0.86 g, activated MnO$_2$) at 0.5 mL min^{-1} with 2 equiv of Hünig's base in CH$_2$Cl$_2$. In-line IR data (collected using an in-line infrared spectrometer) suggested that a typical load of activated MnO$_2$ (10 mmol) could cleanly generate 2 mmol of diazo compound over 40 minutes. The generation of diazo compound, which proved to be

highly practical as the whole process was carried out at room temperature, was followed by an esterification step of the transient species produced.

To explore the general application of this process, different hydrazone derivatives were examined (table **1**). The generated diazo compound was quenched with different carboxylic acids (**3a**-**3c**) and one phenol substrate (**3d**). The reaction was compatible with both electron poor and electron rich aromatic hydrazones (**3d**-**3g**). Electron poor aryl diazo compound gave in general better yields as they are more stabilised. Investigation of the reactivity of a vinylic diazo compound revealed the formation of two regioisomers (**3h** and **3h'**) after reaction with excess AcOH. However, when geranyl hydrazone was processed via our protocol only one isomer was obtained, though only in moderate yield (**3j**). On the other hand, diphenyl ketone hydrazone gave ester **3i** in excellent yield.

Table 1. Titration of generated diazo compound to the corresponding esters.[a]

3a, 73%	3b, 74%	3c, 74%
3d, 56%	3e, 70%	3f, 87%
3g, 43%	3h, 48%	3i, 100%

3h/3h', 76%[b]	3j, 30%
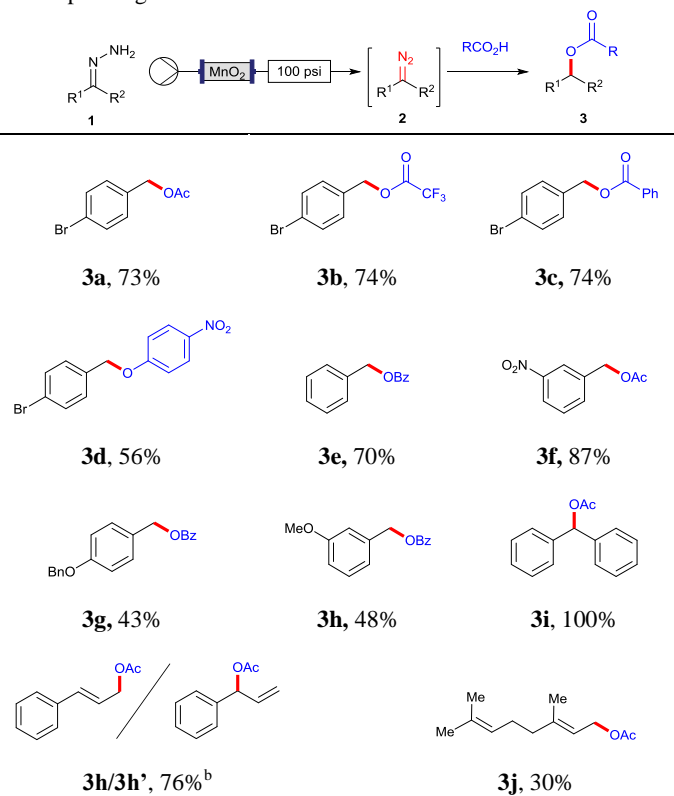
[a]Isolated yield over 3 steps based on aldehyde precursor; [b]combined yield (r.s.=1:1);

Coupling reaction with boronic acids

Diazo compounds are commonly proposed as intermediates for several useful transformations, in particular carbon carbon sp^2-sp^3 coupling between tosylhydrazone and boronic acids.[13a,b,d] High temperature and an inorganic base are typically required as the generation of the diazo compound is reported to be the limiting step of these reactions. We speculated that with our new protocol the chemical reactivity of diazo compounds could be studied separately without interference from the generation step. Pleasingly, after its generation, the stream of the diazo compound **2a** reacted quickly at room temperature with boronic acid **7a** in the first attempt, giving the coupled product **8a** in very good yield (Scheme 4). This extremely mild and fast reaction conditions demonstrated the high

chemical reactivity of diazo compounds and highlighted the advantages of the flow protocol for these reactive intermediates where the equivalent batch mode reaction was found to be unsuccessful.
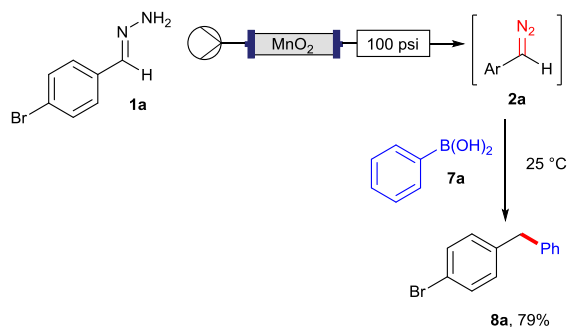
Scheme 4. Flow generation, translocation and reaction of **2a** with **7a**.

Different coupling combinations were investigated using the flow procedure for the generation of clean diazo compounds (table **2**). With much milder reaction conditions compared to the original Barluenga coupling, the electronic properties exerted a strong influence on the reaction time. For electron rich or neutral boronic acids the transformation was complete within 1 hour (compounds **8a-d**). By contrast, electron poor aryl boronic acids required longer reaction time or harsher reaction conditions (**8e-f**). Similar trends were observed with other diazo compounds. Electron poor (more stabilised) diazo compounds required, in general, longer reaction times when reacted with the same boronic acid (**8j**). Interestingly, vinyl diazo compounds are also compatible with this protocol giving the desired products in good yields (**8n-p**). Notably, in these cases a mixture of products was obtained resulting from a 1,3-borotropic rearrangement and the regioselectivity of the products mixtures was strongly influenced by the electronic properties of the two aromatic rings, ranging from 2:1 (**8n**) to 15:1 (**8p**). Different functionalities are tolerated such as halogens, nitro groups and ethers. Heterocycles such as pyridine (**8e**) are also compatible with this protocol. The highly reactive geranyl diazo gave the geranylated product (**8l**) in good yield, based on the titration of the corresponding diazo compound. This process is remarkable as it provides a complementary method for geranylation, where the normal Friedel Crafts alkylation fails. Additionally, we were able to access sp^2-sp^3 coupling transformations for aryl-alkyl diazomethane derivatives in quite good yield (**8m**).
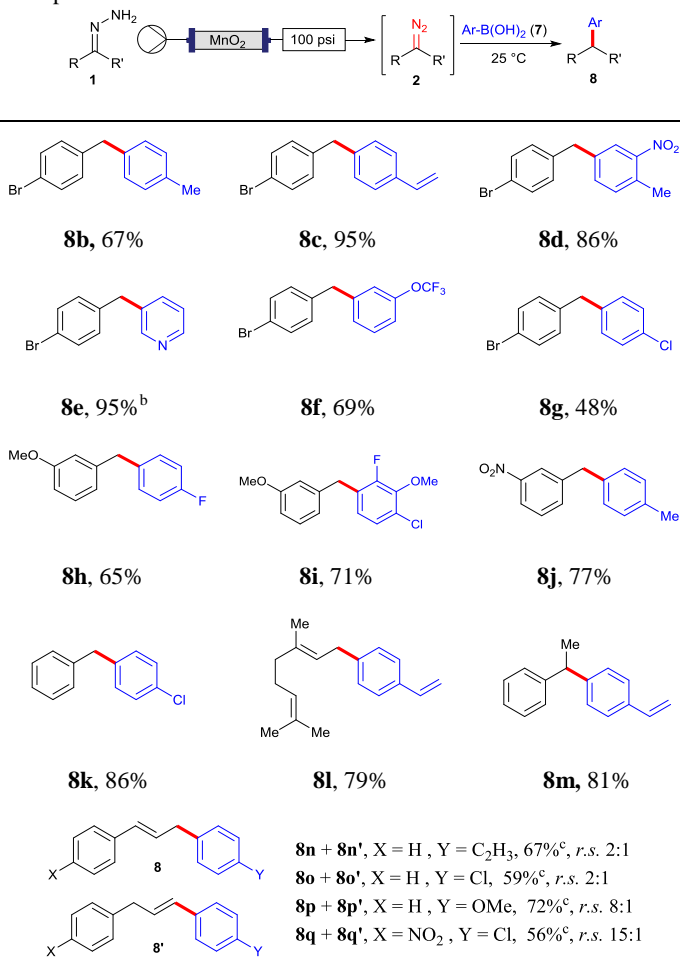
Since the boronic acids are often the more functionalised of the two starting materials, the flow-generated diazo partner was used in excess to fully convert the boronic acid **7b** to the desired coupling product (Scheme 5). Pleasingly, the diaryl compound **8f** was obtained in 96% isolated yield using only a slight excess of diazo compound (1.5 equiv.). In this case, the excess diazo was subsequently quenched using *via* an acidic aqueous work-up protocol. The main by-products detected were both the corresponding azine and alcohol.

The strong dependence of the reaction kinetics on the electronic properties of both starting materials reveals some insight about the reaction mechanism. It is generally assumed that after nucleophilic attack of the diazo compound to the boronic acid, a first ate complex **9** is formed. This intermediate rapidly undergoes a 1,2-carbon migration forming the boronic species **10** which isomerises to the most stable isomer prior to a proto-deboronation to give the coupling product **8** (Scheme 6). Although this mechanism is assumed to describe the actual chemical combinations of the
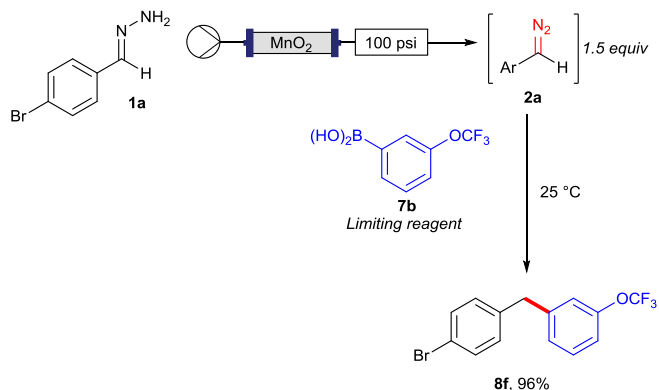
intermediates involved, no report has either identified the kinetics of this kind of transformation or the nature of the species involved. The reasons behind this are linked to the harsh conditions employed to generate the reactive intermediate.[13] We started by investigating the kinetics involved in the sequence of events. Initial NMR studies focused on a model reaction between diazo compound **2b** and boronic acid **7b** and the analysis showed a two-step mechanism (Scheme 6), where the first step happens at a much faster rate than the second one. Using the data collected over a large series of dynamic experiments, we were able to define that the reaction is first order with respect to the diazo compound.

Remarkably, using our mild flow protocol we were also able *for the first time* to *intercept the secondary boronic intermediate* **10**, proving the presence of this intermediate prior to proto-deboronation. Indeed, we envisaged that the generation of a relatively stable boronic intermediate **10** would reduce the rate of proto-deboronation and this new reactive intermediate could be intercepted *via* an alternative reaction pathway. This idea was realised with the use of acetophenone hydrazone (**1b**) as starting material, which was passed through the oxidant-column, packed with activated MnO_2, to form the corresponding diazo compound (as detected by in-line IR); the transient diazo species was translocated to react with boronic acid **7a** and then further reacted with a solution of hydrogen peroxide. The analysis of the material revealed the prevalence of alcohol **11** (68%) within the mixture, corroborating the presence of a boronic species **10c** as an intermediate.
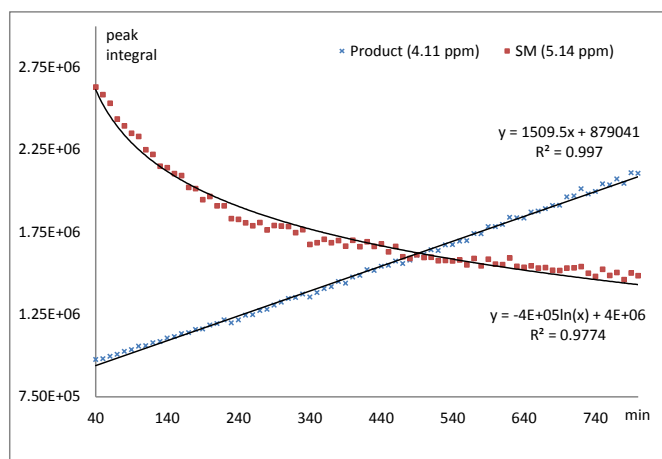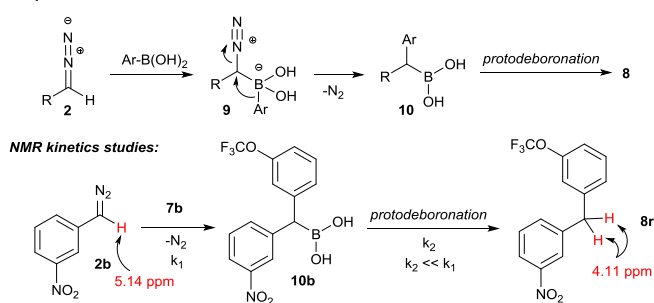
Table 2. Coupling products prepared by reaction of diazo compounds with boronic acids.[a]

8b, 67%	**8c,** 95%	**8d,** 86%
8e, 95%[b]	**8f,** 69%	**8g,** 48%
8h, 65%	**8i,** 71%	**8j,** 77%
8k, 86%	**8l,** 79%	**8m,** 81%

8n + **8n'**, X = H , Y = C_2H_3, 67%[c], r.s. 2:1
8o + **8o'**, X = H , Y = Cl, 59%[c], r.s. 2:1
8p + **8p'**, X = H , Y = OMe, 72%[c], r.s. 8:1
8q + **8q'**, X = NO_2 , Y = Cl, 56%[c], r.s. 15:1

Scheme 5. Boronic acid **7b** used as limiting reagent.
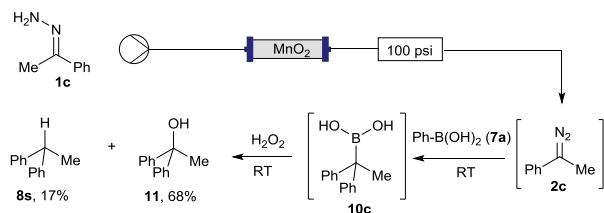
Scheme 6. Mechanistic studies of coupling reaction between diazo compound and boronic acid.

To increase the efficiency of the new protocol, the regeneration and re-use of MnO_2 column was briefly investigated. The spent manganese oxide could be oxidised by passage of a solution of *tert*-butyl hydroperoxide (TBHP, 1M in CH_2Cl_2) (**Scheme 7**). Interestingly, the regenerated column produced diazo compound without the need for a pre-conditioning phase. The heterogeneous oxidant was recycled over three different cycles with just a slight decrease in reactivity after each recycle as detected by in-line IR (**Figure 1**).
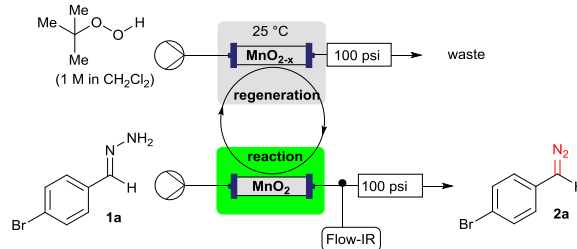
Scheme 7. Flow regeneration of MnO_2 reagent using TBHP.
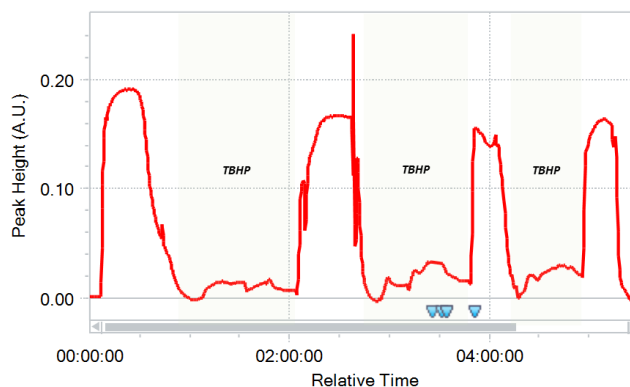
Figure 1. IR data for the four regeneration cycles of oxidation for a single MnO_2 load (0.86 g).

Moreover, in a preliminary attempt with tube-in-tube technology,[16] oxygen gas also proved to be a useful re-oxidant for a low cost regeneration of MnO_2 but with lower efficiency.[17]

Conclusion

In summary, we have reported a practical flow generation of *unstable* diazo compounds as reactive intermediate using the cheap, recyclable and non-toxic oxidant, MnO_2. The diazo flow stream can be accurately titrated or followed by in-line IR. Using our protocol, we were able to deliver sp^2-sp^3 coupling reactions of the freshly generated diazo species with boronic acids, under extremely mild and simple reaction conditions providing alkylated products in good to excellent yield. The mechanistic studies demonstrated for the first time the presence of a specific boronic intermediate. These results demonstrate that flow generation/translocation/reaction of transient species opens up opportunities for the exploitation and study of new chemical reactivities. Further studies in this area are underway in our laboratories.

Acknowledgements

Notes and references

[a] Innovative Technology Centre, Department of Chemistry University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK

[b] Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06340, USA.

1   a) S. V. Ley, *Chem. Rec.*, 2012, **12**, 378–390; b) R. M. Myers, D. E. Fitzpatrick, R. M. Turner and S. V. Ley, *Chem. Eur. J.* 2014, **20**, 12348–12366.

2   a) M. Doyle, *Acc. Chem. Res.* 1986, **19**, 348–356; b) A. J. Padwa *Organomet. Chem.* 2001, **617**, 3–16; c) M. Regitz and G. Mass, In *Diazo Compounds Properties and Synthesis*, Academic Press, Inc., Orlando, 1986; c) M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, 1998 d) J. N. Johnston, H. Muchalski and T. L. Troyer *Angew. Chem. Int. Ed.*, 2010, **49**, 2290–2298.

3   a) R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, (Ed. A. Padwa), Wiley, New York, 1984 b) G. Mass, In *Heterocyclic Compounds: 1,3-Dipolar Cycloaddition*, Vol. 59 (Eds.: A. Padwa, W. H. Pearson), John Wiley and Sons, Inc., New York, 2002, pp 541–621.

4   Selected examples for carbonyl homologation: a) C. D. Gutsche, *Org. React.* 1954, **8**, 364–429; b) C. R. Holmquist and E. J. Roskamp, *J. Org. Chem.* 1989, **54**, 3258–3260; c) D. C. Moebius and J. S. Kingsbury *J. Am. Chem. Soc.*, 2009, **131**, 878–879; d) D.M. Allwood, D.C. Blakemore and S.V. Ley, *Org. Lett.,* 2014, **16**, 3064–3067.

5   Selected examples for cyclopropanation: a) V. K. Aggarwal, J. de Vicente and R. V. Bonnert, *Org. Lett.* 2001, **3**, 2785–2788; b) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette *Chem. Rev.* 2003, **103**, 977−1050; c) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183–190; c) S. R. Goudreau and A. B. Charette, *J. Am. Chem. Soc.*, 2009, **131**, 15633–15635.

6   a) G. Maas *Angew. Chem. Int. Ed.*, 2009, **48**, 8186–8195; b) V. L. Rendina and J. S. Kingsbury, *J. Org. Chem.*, 2012, **77**, 1181–1185; c) A. J. Wommack and J. S. Kingsbury, *J. Org. Chem.*, 2013, **78**, 10573–10587; d)T. L. Holton and H. Shechter, *J. Org. Chem.*, 1995, **60**, 4725–4729.

7   L. I. Smith and K. L. Howard, *Org. Synth.*, 1944, **24**, 53; b) K. Nakagawa, H. Onoue and K. Minami, *Chem. Commun.*, 1966, 730; c) M. I. Javed and M. Brewer, *Org. Lett.*, 2007, **9**, 1789–1792.

8   a) R. A. Maurya, C. P. Park, J. H. Lee and D.-P. Kim, *Angew. Chem. Int. Ed.* 2011, **50**, 5952–5955; b) B. Morandi and E. M. Carreira *Science,* 2012, **335**, 1471–1474; c) E. Rossi, P. Woehl and M. Maggini *Org. Process Res. Dev.*, 2012, **16**, 1146–1149; flow generation of diazo methane: d) L. D. Proctor and A. J. Warr, *Org. Process Res. Dev.* 2002, **6**, 884–892; e) M. Struempel, B. Ondruschka and A. Stark, *Org. Process Res. Dev.* 2009, **13**, 1014–1021; f) F. Mastronardi, B. Gutmann and C. O. Kappe *Org. Lett.*, 2013, **15**, 5590–5593; g) L. J. Martin, A. L. Marzinzik, S. V. Ley and I. R. Baxendale, *Org. Lett.*, 2011, **13**, 320–323.

9   a) M. Z. Barakat, M. F. Abdel-Wahab and M. M. El-Sadr, *J. Chem. Soc.*, 1956, 4685–4687; b) M. P. Doyle and M. Yan *Arkivoc* 2002, 180–185; c) M. P. Doyle and M. Yan, *J. Org. Chem.* 2002, **67**, 602–604; d) J. R. Denton, D. Sukumaran and H. M. L. Davies, *Org. Lett.*, 2007, **9**, 2625–2628; e) K.-H. Lee and K.-Y. Ko, *Bull. Korean Chem. Soc.*, 2006, **27**, 185–186; f) T. C. Sharma, A. Lal and V. Saksena, *Bull. Chem. Soc. Japan*, 1976, **49**, 2881–2882.

10 a) C. Battilocchio, J. M. Hawkins and S. V. Ley, *Org. Lett.* 2014, **16**, 1060; b) S. Glöckner, D. N. Tran, R. J. Ingham, S. Fenner, Z. E. Wilson, C. Battilocchio and S. V. Ley, *Org. Biomol. Chem.* DOI:10.1039/C4OB02105C.

11 Selected recent reviews for chemical flow systems: a) R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 7502–7519; b) J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.* 2012, **354**, 17–57; c) C. Wiles and P. Watts, *Green Chem.*, 2012, **14**, 38–54; d) L. Malet-Sanz and F. Susanne, *J. Med. Chem.* 2012, **55**, 4062−4098; e) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* 2013, **88**, 519–552; f) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.* 2013, **42**, 8849−8869.

12 Selected recent examples for chemical flow systems: a)H.   Kim, A. Nagaki and J.-I. Yoshida, *Nature Commun.*, 2011, **2**, 264; b) F. Levesque and P. H. Seeberger, *Angew. Chem. Int. Ed.*, 2012, **51**, 1706–1709; c) B. J. Deadman, C. Battilocchio, E. Sliwinski and S. V. Ley, *Green Chem.*, 2013,**15**, 2050–2055; d) Z. He and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **53**, 3353 –3357; e) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.* 2013, **9**, 1613–1619; f) S. Newton, C. F. Carter, C. M. Pearson, L. de C. Alves, H. Lange, P. Thansandote and S. V. Ley *Angew. Chem. Int. Ed.*, 2014, **53**, 4915–4920; g) J. Hartwig, S. Ceylan, L. Kupracz, L. Coutable and A. Kirschning, *Angew. Chem. Int. Ed.*, 2013, **52**, 9813–9817; h) A. M. Nightingale, T. W. Phillips, J. H. Bannock and J. C. de Mello, *Nature Commun.*, 2014, **5**, 3777; i) X. Fan, V. Sans, P. Yaseneva, D. D. Plaza, J. Williams and A. Lapkin, *Org. Process Res. Dev.* 2012, **16**, 1039−1042.

13 Selected recent examples for metal free sp^2-sp^3 cross-coupling: a) J. Barluenga, M. Tomás-Gamasa, F. Aznar and C. Valdés,   *Nat. Chem.* 2009, **1**, 494−499; C. Peng, W. Zhang, G. Yan and J. Wang *Org. Lett.*, 2009, **11**, 1667–1670; b) S. Nakagawa, K. A. Bainbridge, K. Butcher, D. Ellis, W. Klute and T. Ryckmans, *ChemMedChem* 2012, **7**, 233−236; M. C. Pérez-Aguilar and C. Valdés *Angew. Chem. Int. Ed.*, 2012, **51**, 5953−5957 c) L. Kupracz and A. Kirschning, *J. Flow Chem.*, 2013, **3**, 11−16; d) D.M. Allwood, D.C. Blakemore, A.D. Brown and S.V. Ley, *J. Org. Chem.* 2014, **79**, 328–338; e) D.M. Allwood, D.C. Blakemore and S.V. Ley, *Org. Lett.* 2014, **16**, 3064-3067; f) G. Wu, Y. Deng, C. Wu, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201406765; g) G. Wu, Y. Deng, C. Wu, X. Wang, Y. Zhang and J. Wang *Eur. J. Org. Chem.* 2014, 4477–4481; h) *Metal Free C-H functionalization of aromatics (Top. Heterocylc. Chem, 37, 2014)*, (Ed. V. Charushin, O. Chupakhin), Springer, Switzerland, 2014.

14 Any aryl hydrazone can be used for conditioning the column.

15 We are currently investigating the mechanism of oxidation. We speculate that the oxidative process proceeds *via* either ionic or radical pathways.

16 Selected examples for tube-in-tube gas reactions: a) S. Newton, S.V. Ley, E.C. Arce and D. Grainger *Adv. Synth. Catal.* 2012, **354**, 1805-1812; b) P.B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López and S.V. Ley *Org. Biomol. Chem.* 2012, **10**, 5774-5779; c) T.P. Peterson, A. Polyzos, M. O'Brien, T. Ulven, I.R. Baxendale and S.V. Ley *ChemSusChem* 2012, **5**, 274-277; d) S.L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D.X. Hu, R.W. Bates, B. Martin, B. Schenkel and S.V. Ley, *ChemCatChem*, 2013, **5**, 159-172; e) F. Mastronardi , B. Gutmann, and C. O. Kappe *Org. Lett.*, 2013, **15**, 5590–5593; f) B. Tomaszewski, A. Schmid and K. Buehler, *Org. Process Res. Dev.*, doi: 10.1021/op5002116; g) U. Gross, P. Koos, M. O'Brien, A. Polyzos and S.V. Ley, *Eur. J. Org. Chem.*,2014, 6418-6430.

17 Depleted oxidant-activity column was flushed with a tube-in-tube system using oxygen 6% during 5h. This column showed enhanced activity by producing diazo compound at ca. 25% yield (evaluated by IR).