ABSTRACT: Generation and use of trifllyl azide in flow enables efficient synthesis of a range of α-diazocarbonyl compounds, including α-diazoketones, α-diazoamides, and an α-diazosulfonyl ester, via both Regitz-type diazo transfer and deacylative/debenzoylative diazo-transfer processes with excellent yields and offers versatility in the solvent employed, in addition to addressing the hazards associated with handling of this highly reactive sulfonyl azide. Telescoping the generation of trifllyl azide and diazo-transfer process with highly enantioselective copper-mediated intramolecular aromatic addition and C−H insertion processes demonstrates that the reaction stream containing the α-diazocarbonyl compound can be obtained in sufficient purity to pass directly over the immobilized copper bis(oxazoline) catalyst without detrimentally impacting the catalyst enantioselectivity.

INTRODUCTION

The transition-metal-catalyzed reactions of α-diazocarbonyl compounds are among the most versatile transformations in organic synthesis.1−5 In particular, enantioselective rhodium- and copper-catalyzed processes have attracted significant attention, facilitating the efficient formation of new C−C bonds, among other transformations, in a highly diastereoselective and enantioselective fashion, including C−H insertion,4,5 aromatic addition reaction,1 and cyclopropanation.6−8

Within our research team, highly enantioselective copper-catalyzed C−H insertions, employing bis(oxazoline) ligands, have been reported across a range of substrates leading to thiopyran S,S-dioxides (up to 98% ee),9 sulfolanes (up to 80% ee),10 cyclopentanones (up to 82% ee),11 and β- and γ-lactams (up to 82% ee),12 with particular success using sulfonyl-substituted α-diazoketones and α-diazoesters. Extension of this work to copper-mediated desymmetrization proved highly effective, resulting in formation of the desymmetrized thiopyran S,S-dioxide in up to 98% ee.13

Furthermore, the same copper–bis(oxazoline) catalysts have been employed in intramolecular Buchner additions (Scheme 1),14−19 leading to azulenones with excellent enantiocontrol (up to 95% ee);20 the azulenones exist in a dynamic equilibrium of the norcaradiene (NCD) and cycloheptatriene (CHT) forms through reversible electrocyclic ring opening/closing, as evidenced by time-averaged1H NMR signals.20,21 Formation of the quaternary bridgehead stereocenter with excellent enantiofacial control through use of the copper bis-oxazoline catalysts is very attractive from a synthetic perspective.

Despite the synthetic versatility of α-diazocarbonyl compounds, their use at scale has been limited by safety concerns around the potentially hazardous nature of these compounds and, more particularly, their sulfonyl azide or diazoalkane precursors.22,23 For example, the practical synthetic utility of the copper-mediated intramolecular Buchner research in Scheme 1 is impacted by the requirement to utilize a diazoalkane, in this instance diazoethane, to generate the α-diazoketone. To address this challenge, efforts have been made to establish continuous processing methodologies for in situ generation and use of diazo compounds and, by extension, for
in situ preparation of the requisite diazo-transfer reagents. \(^{24-28}\) Of the reports of the diazo-transfer process in flow, however, most have employed sulfonyl azides directly as reagents. \(^{29-32}\) The improved safety profile associated with the handling and use of hazardous compounds in flow chemistry platforms has been a critical aspect of the increasing emergence of these technologies. Enhanced process control, \(^{24,32-37}\) due to automation, in-line reaction monitoring, and the superior efficiency of mass and heat transfer in continuous processes—principally, a consequence of the high surface-area-to-volume ratios inherent in pipe or tube reactors—together with the specific facility for immediate use of hazardous material, generated in situ in minimal quantities, \(^{38}\) has enabled synthetic chemistry approaches that would previously have been dismissed due to the associated risks at large scale.

Wirth has reported a two-step telescoped process where batch-generated sulfonyl azide was used for diazo transfer to an aryl ester 1 which, following liquid—liquid separation, was flowed into a round-bottom flask containing a rhodium(II) catalyst, affording a racemic cyclopropanation product 2 (Scheme 2A). \(^{29}\) Wirth’s method included a drying trap with MgSO\(_4\), which notably improved yield, although side product formation was still observed.

To overcome the requirement to synthesize (in advance) and handle sulfonyl azides, we have demonstrated successful in situ generation of tosyl or mesyl azide in flow telescoped with diazo transfer to a range of substrates in good to excellent yields and including development of a sodium acetylacetonate quench system to remove any unreacted sulfonyl azide from the reaction outflow following the diazo transfer. \(^{39,40}\) As illustrated in Scheme 2B, the generation of mesyl azide, diazo transfer to the \(\beta\)-ketoester 3, and subsequent transformation of the \(\alpha\)-diazocarbonyl compounds 4 in a thermal Wolff rearrangement with trapping of the ketene by methanol has been successfully telescoped in a continuous flow process establishing that \(\alpha\)-diazocarbonyl compounds can be generated and used in flow without isolation and handling of either the \(\alpha\)-diazocarbonyl compounds or, critically, the sulfonyl azide precursors.

Subsequently, Monbaliu has described a telescoped process for the synthesis of BOC-protected methylphenidate, starting with in situ TsN\(_3\) preparation followed by Regitz diazo transfer and rhodium(II) octanoate catalyzed intermolecular C–H insertion leading to the product 7 in 19% yield (Scheme 2C). \(^{41}\) An alternative telescoped synthesis was also reported whereby the thermolysis of a tosyl hydrazone followed by intramolecular C–H insertion and \(\beta\)-lactam methanolysis afforded the deprotected derivative of 7 in a much improved yield of 70%. \(^{41}\)

Over the past two decades, there has been tremendous progress in immobilization of rhodium carboxylate and carboxamidate catalysts, \(^{42-47}\) with significant contributions from Davies, \(^{48-51}\) Doyle, \(^{52,53}\) and Hashimoto, \(^{54}\) among others.
Davies has reported in situ formation of aryl α-diazoesters in flow, via oxidation of the corresponding hydrazones, followed by telescoped intermolecular cyclopropanation or C–H insertion with an immobilized rhodium(II) carboxylate catalyst. Excellent yields and enantioselectivities were reported which matched the results from the corresponding batch reactions.

Copper-catalyzed transformations utilizing heterogeneous immobilized bis(oxazoline) ligands have also been investigated, including the immobilization of a (4S)-Ph-bis(oxazoline) ligand onto laponite clay by electrostatic interactions, which was used in the intermolecular C–H insertion into THF. Only a handful of reports, however, have described immobilized copper-catalyzed transformations of α-diazocarbonyl compounds performed in flow. Following the precedent of Burguete for generation of an insoluble polymer bound (IPB) copper–bis(oxazoline) catalyst, our group has demonstrated its use for enantioselective intramolecular Buchner reactions in batch and using continuous flow processing, in up to 83% ee (Scheme 2D). Critically, the immobilized copper catalyst could be washed and reused a number of times.

To the best of our knowledge, however, a fully telescoped continuous flow process involving formation of the sulfonyl azide followed sequentially by diazo transfer and a copper-catalyzed process has not been reported to date. A key challenge is to ensure that the reaction outflow from the diazo transfer is amenable to direct exposure to the enantioselective transition-metal catalyst. In particular, removal of any reaction components from the diazo-transfer process—sulfonamide, base, and any unreacted sulfonil azide—that could negatively impact on the transition-metal-catalyzed transformation through metal leaching, catalyst poisoning, or complexation leading to reduced activity and/or enantioselectivity must be addressed; in addition, the removal of water is critical to avoiding competing O–H insertion pathways. Furthermore, for efficient telescoping, conducting the sulfonil azide generation, prior to the diazo transfer, in a solvent which is compatible with the enantioselective transition metal-catalyzed step is critically important.

In general, it is evident that any telescoped process using diazo compounds, generated in flow, in a downstream transition-metal catalysis requires a diazo feed stream that is (1) in a suitable solvent for the desired transition metal-catalyzed process, (2) free of any byproducts and reagents from upstream processes, and (3) sufficiently dry to undergo water-sensitive transformations.

Our objective was, therefore, to further develop our earlier telescoped continuous sulfonyl azide synthesis and diazo-transfer methodologies, which did not completely fulfill these criteria (vide infra), to deliver a process that would enable the in situ generation of α-diazoketones through diazo transfer to be directly linked with copper-catalyzed downstream transformations utilizing IPB copper—BOX catalyst. Specifically, aromatic addition and C–H insertion were the transformations of interest. As part of this work, we also wished to develop a versatile route which could be employed for the synthesis of α-diazoketones such as those illustrated in Scheme 1, possessing a simple methyl substituent, but also for more diverse α-diazocarbonyl compounds bearing additional substituents, including α-diazo-β-ketonitriles.

Herein, we report the successful telescoping of triflyl azide generation and use in the synthesis of a range of different α-diazocarbonyl compounds including α-diazoketones 8, 11–13, an α-diazolactam 29, α-cyano-α-diazocetamides 55–62, an α-diazo-β-ketonitrile 38, and an α-diazo sulfonyl ester 63 and demonstration of their direct use in three enantioselective copper-mediated transformations, thereby establishing the feasibility of this approach.

RESULTS AND DISCUSSION

α-Diazoketones 8 and 11–13 were selected for the initial investigations in this work, with a view to telescoping the in situ generation of these acylation products with their direct use in copper-catalyzed aromatic addition in continuous flow. Prior to this work, the diazoethane acylation route to α-diazoketones 8 and 11–13, summarized in Scheme 3, has been utilized rather than diazo transfer (in order to overcome the insufficient activation afforded by a single ketone group), but while effective, this route suffers from a number of challenges; these include the safety hazards associated with diazoethane and its precursor, N-ethyl-N-nitrosourea, which limit its scalability. Furthermore, this process affords the α-diazoketones in diethyl ether, while dichloromethane is the usual choice of solvent for copper-catalyzed aromatic additions. An alternative method that avoids the use of diazoalkanes and which is more versatile in the choice of solvent was, therefore, highly desirable, enhancing compatibility with downstream reactions.

Debenzyloative diazo transfer for preparation of α-diazoketones 8 and 11–13, as pioneered by Taber, was explored (Figure 1); an adaptation of this route for a continuous flow platform would offer significant advantages over the diazoethane acylation route, obviating use of hazardous diazoalkanes and dramatically improving the safety profile of the process. Dichloromethane is typically employed as the reaction solvent for these transformations, which would be compatible with subsequent telescoped aromatic addition or C–H insertion, while allowing further scope to use alternative solvents instead. This proposed route would exploit...
sulfonyl azide diazo-transfer reagents, which the group has experience in generating and using in flow.\textsuperscript{36,40}

**Synthesis of α-Diazo Ketones by Debenzyolative Diazo Transfer.** Initial studies focused on debenzyolative diazo transfer to β-diketone 19 (prepared via the corresponding acyl benzotriazole\textsuperscript{65}) conducted in batch, prior to investigation in flow. Thus, 2,5-dimethyl-1,5-diphenylhexan-1,3-dione (19) was transformed to α-diazo ketone 11, employing DBU as base and p-nitrobenzenesulfonyl azide (p-NBSA) as diazo-transfer reagent in dichloromethane at 0 °C (Scheme 4), in an adaption of Taber’s original route.\textsuperscript{65} Purification of α-diazo ketone 11 proved challenging due to coelution with the sulfonyl benzamide byproduct resulting in 37% yield, which was later improved through alteration of the sulfonyl azide (vide infra).

Extending this process to flow (Table 1, entry 1) was first undertaken using peristaltic pumps matching the “in batch” reaction conditions with the exception of temperature; the reaction was performed at room temperature for convenience due to the favorable dissipation of heat in continuous flow. A residence time of 1 h proved sufficient for complete consumption of the starting material. As the outflow of the diazo transfer was ultimately envisaged to be directly used in a transition-metal-catalyzed reaction, it was important to remove DBU from the reaction stream to prevent complexation with metal catalysts, compromising the subsequent transformation. Accordingly, the reactor effluent was flowed through a plug of silica gel prior to collection. As with the batch process, it proved challenging to completely remove the sulfonyl benzamide byproduct and 11 was afforded in a comparable 36% yield; this result confirmed, however, that conducting this diazo transfer in continuous flow and passing the effluent through silica gel had no detrimental impact on the reaction outcome.

As summarized in Table 1, investigation of a range of bases was undertaken, none of which led to a better outcome than DBU. Interestingly, diazo transfer was not observed when immobilized DBU was used. Use of sodium hydride, which had proved effective under batch conditions,\textsuperscript{68} could not be readily employed in flow.

An improved yield (54%, Table 1, entry 8) was observed when the temperature in the reactor coils was elevated to 45 °C. Methanesulfonyl azide (MsN\textsubscript{3}) proved to be a poor choice of diazo-transfer reagent for this transformation; however, use of p-toluenesulfonyl azide (TsN\textsubscript{3}) (53%, Table 1, entry 10) gave a result comparable to that of p-NBSA (Table 1, entry 8). TsN\textsubscript{3} was also a more judicious choice of diazo-transfer reagent than p-NBSA as its sulfonyl benzamide byproduct was more easily removed during flash chromatography, allowing clean fractions of α-diazo ketone 11 to be more readily obtained. Using this methodology, employing TsN\textsubscript{3} on continuous flow, the aryl-substituted α-diazo ketones 8, 12, and 13 were afforded in similar yields from their corresponding 1,3-diketones and DBU (Scheme 5). Despite the encouraging results with these improved conditions, the yields obtained remained moderate at best (11, 53%, Table 1, entry 10 cf. 37% in batch, Scheme 4 vs 83% for diazoethane acylation from the acid chloride, Scheme 3).

As the reaction was envisaged to be part of a telescoped process, the diazo-transfer reagent would ideally be generated in the solvent to be used in the downstream diazo transfer and copper-catalyzed transformations; aromatic addition reactions are typically conducted in dichloromethane with a significant decrease in chemo- and enantioselectivity observed with other solvents.\textsuperscript{14} In particular, acetonitrile has been found to inhibit homogeneous copper–bis(oxazoline) catalysis of aromatic

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**Table 1. Optimization of Debenzyolative Diazotransfer to Diketone 19 in Flow**

| entry | base                  | sulfonyl azide | temp (°C) | yield (%) |
|-------|-----------------------|----------------|-----------|-----------|
| 1     | DBU                   | p-NBSA         | rt        | 36        |
| 2*    | Amberlyst A21        | p-NBSA         | rt        | b         |
| 3*    | polymer-bound DBU    | p-NBSA         | rt        | b         |
| 4     | triethylamine         | p-NBSA         | rt        | b         |
| 5     | tetramethylenediamine| p-NBSA         | rt        | 18        |
| 6     | 1,4-diazabicyclo[2.2.2]octane | p-NBSA | rt | b |
| 7     | N,N-dioisopropylthylamine | p-NBSA | rt | b |
| 8     | DBU                   | TsN\textsubscript{3} | 45       | 54        |
| 9     | DBU                   | MsN\textsubscript{3} | 45       | 25        |
| 10    | DBU                   | TsN\textsubscript{3} | 45       | 53        |

*Solid base was packed in a 6.6 mm diameter glass column, and the combined 1,3-diketone 19/ p-NBSA stream was passed through it.\textsuperscript{6} No signals for α-diazo ketone product 11 were observed in the \textsuperscript{1}H NMR spectrum of the crude product mixture; only unreacted starting material 19 was recovered.
addition and to be incompatible with the IPB copper catalyst, causing leaching of copper. Tosyl azide is prepared in flow in aqueous acetonitrile, or NMP, and in batch in aqueous acetone, solvents which are not readily compatible with transition-metal catalysis downstream.

Tri fluoromethanesulfonyl azide (22) (triflyl azide, TfN₃) is a powerful diazo-transfer reagent that reacts even with highly stabilized acceptor molecules. In addition to its potent reactivity, it is versatile due to the variety of organic solvents in which it can be generated, including dichloromethane, toluene, hexane, acetonitrile, pyridine, MeOH, and EtOH; this is a desirable attribute for diazo transfers that are part of telescoped processes and which necessitate the α-diazocarbonyl compound to be in a requisite solvent for the “end-of-line” transformation. However, there are inherent risks associated with triflyl azide (22) and its byproducts and extreme caution should be exercised during its preparation and use; it is a toxic compound and is known to detonate if not handled correctly. Where appropriate procedures are followed, however, it can be used in a safe manner (see the Supporting Information (SI) for further discussion on safety considerations on using triflyl azide in flow), facilitating the preparation of many otherwise difficult-to-access diazo substrates.

Triflyl azide (22) is prepared by the reaction of triflic anhydride with sodium azide. For the purpose of this work, the “in batch” preparation of triflyl azide (22) was carried out using a slightly modified version of the procedure reported by Xu, whereby the sulfonyl azide was generated with sodium azide (5.0 equiv) and triflic anhydride (1.1 equiv relative to 19) in a biphasic (2:1) water/dichloromethane mixture at 0 °C for 2 h. The layers were separated, and then the dichloromethane solution of triflyl azide (22) was used directly in the diazo-transfer step (Scheme 6).

There are important safety and process considerations when carrying out the process shown in Scheme 6. Triflyl azide (22) should never be isolated in pure form, and the organic solvent should not be removed from its solutions, as this is known to lead to detonation. The separated organic phase was washed with aqueous sodium bicarbonate to neutralize any triflic acid that may be present and which could degrade the subsequent α-diazoketone products. The resulting triflyl azide solution was added slowly (20–30 min) to a dichloromethane solution of 1,3-diketone 19 and DBU at room temperature, and reaction progression was monitored by IR spectroscopy. After 2 h, complete disappearance of the azide stretch (∼2150 cm⁻¹) was observed, and the pure α-diazoketone 11 (ν(C= N₂): 2061 cm⁻¹) was isolated in 65% yield. The excess of sodium azide
used in the reaction and remaining in the aqueous layer was
quenched by the literature method.  

Given this much improved yield for the debenzyloative diazo
transfer through use of triflyl azide, the diazo-transfer element
of the process was initially trialled in flow (Scheme 7). Triflyl
azide (22) was generated in batch, as described above (Scheme
6); the resulting dichloromethane solution of triflyl azide (22)
was pumped to a T-piece to meet a solution stream of 19 and
DBU, and then the combined stream was pumped through a
coiled reactor for a residence time of 2 h at room temperature.
Use of a peristaltic pump proved effective, while HPLC
(piston) pumps were found to be less effective. The orange
effluent stream was passed through a silica gel plug, collected,
and checked by IR spectroscopy to verify complete
consumption of triflyl azide (22) prior to concentration.

The desired α-diazoketone 11 was afforded in 93% yield
after chromatography. 19F NMR spectra were recorded for the
isolated product to ensure that no residual triflyl azide or other
fluorinated byproducts, without observable signals in the 1H
NMR spectrum, were present. There is one report in the
literature of the byproduct trifluoromethylsulfonyl benzamide
(δF ≈ 76.97); this compound was not observed or isolated
during this work and was presumably retained on the silica gel.

This increase in yield (up to 93%, from 65% for the batch
process (Scheme 6) and 53% for the tosyl azide mediated
transformation (Table 1, entry 10)) was a significant
breakthrough and effectively represented optimized conditions
for diazo transfer to form 11 in continuous flow. The improved
outcome in flow vs batch can be rationalized due to the
superior process control achieved in flow, in this instance,
the control over reactant ratios and temperature, specifically
the consistent manner in which reagents were combined during
the continuous process.

Telescoped Debenzyloative Diazotransfer in Flow.
Having established that use of triflyl azide in flow for diazo
transfer was effective, the next challenge was to telescope the
preparation of this hazardous reagent in flow with the diazo-
transfer step. As illustrated in Scheme 8, the formation of triflyl
azide (22) and subsequent use in debenzyloative diazo transfer
to 1,3-diketones 18–21 proved successful, enabling the use of
triflyl azide as a powerful reagent for diazo transfer while
obviating the need for isolation or handling of this reagent.
Focusing on the generation of triflyl azide in flow, based on the
Xu procedure for batch preparation of triflyl azide (22) 71
and the successful use of a dichloromethane solution of 22 for
diazo transfer in flow (Scheme 7), generation of triflyl azide
(22) in flow was initially implemented in dichloromethane.
Thus, an aqueous solution of sodium azide was pumped to a
T-piece to meet a dichloromethane solution of triflic anhydride
with the combined biphasic stream passed through a reactor
coil for a residence time of 1 h. To avoid the reaction of triflic
anhydride with adventitious water, the dichloromethane
solution was freshly prepared before use, and any hydrolysis
was effectively reduced by charging the reagent solutions at 3
mL min−1 to minimize exposure to air during the transfer.
The reaction stream then joined a stream of saturated aqueous
sodium bicarbonate to remove any triflic acid, and the
combined biphasic effluent was then separated by an in-line
liquid–liquid separator.

The reactant ratios for this process were determined by prior
experiments involving diazo transfer to a known excess of
sodium acetylacetonate hydride (see the SI for further details),
which indirectly established the efficiency of formation of triflyl
azide (22) as 58% by measuring the extent of diazo transfer to
the β-diketonate 6 to form 23 (as shown, more generally, in
Scheme 9), without having to isolate and quantify the
hazardous sulfonyl azide. The ratio of triflic anhydride to
1,3-diketone 19 required to execute a telescoped synthesis of
α-diazoketone 11 in flow, therefore, was estimated to be 1.7:1.
respectively. Scheme 8 outlines the continuous flow setup used for the telescoped synthesis of trifly azide (22) and subsequent debenzyolative diazo transfer to 1,3-diketones 18–21, 24, and 25. As was noted for the trifly azide solution (vide supra), use of a peristaltic pump was required.

The conditions for the preparation of trifly azide (22) for this diazo transfer in flow were chosen to deliver similar reactant ratios and concentrations to those successfully employed for the process with pregenerated trifly azide (22) in Scheme 7. The stream containing the trifly azide after the phase separation was mixed with the solution containing the substrate and DBU and passed through a reactor coil for 2 h. The effluent from the diazo transfer was again pumped through a column reactor of silica gel at room temperature (for removal of polar reaction components), and the collected reaction solution was checked by IR spectroscopy to ensure complete consumption of trifly azide (22). The process was first implemented for debenzyolative diazo transfer to diketone 19, and gratifyingly, α-diazoketone 11 was isolated reproducibly in 80% yield, albeit slightly lower than the yield recorded for the flow process using a “preformed” trifly azide solution (93%, Scheme 7). This result, however, was still a considerable improvement on other batch diazo-transfer processes investigated with alternative diazo-transfer reagents during this work. The reduced yield for the telescoped method is most likely due to the presence of residual water in the organic stream, compared to the pregenerated solution of trifly azide in Scheme 7, which was dried when prepared in batch prior to use in the diazo transfer. For later telescoped processes, involving downstream transition-metal catalysis, this observation was addressed through incorporation of a drying agent into the process (vide infra).

On the basis of the successful synthesis of α-diazoketone 11 using this telescoped preparation of trifly azide (22) and subsequent diazo transfer in flow, this process using identical conditions was applied to each of the other precursors identified for this study at the outset, namely 1,3-diketones 18, 20, and 21 (Scheme 8), with good yields achieved for α-diazoketones 8, 12, and 13 (70–80%, after chromatography). The flow process was also used to synthesize novel α-diazoketones 26 and 27 in excellent yields (80% and 91%, respectively) from their 1,3-diketone precursors 24 and 25 (Scheme 8), indicating that the process is efficient even when the steric demand of the alkyl substituent at the site of reaction is increased. The flexibility of this route to α-diazoketones bearing different substituents on the diazo carbon is a clear advantage, avoiding generation and use of a series of diazoalkanes to access differently substituted α-diazoketones. The precursor diketones 24 and 25 were readily accessed using the route employed for 19.

The yields obtained for the telescoped flow process with trifly azide (22) were generally comparable with those of the diazoethane acylation route (from the preformed acid chlorides), although in the case of the 4-fluoro α-diazoketone 13, the yield from the telescoped TfN₃ flow process offered a far superior yield (Table 2, entry 4, 70% vs 38%). Previously, we reported the synthesis of α-diazoketone 13 in just 38% yield. The yields for the telescoped trifly azide flow process were also higher than those recorded when using batch prepared tosyl azide as diazo-transfer reagent in flow. Notably, the yields of 11 and 13 obtained using the telescoped TfN₃ flow process were higher than those obtained using TfN₃ 22 in the corresponding batch reaction, highlighting a synthetic advantage in addition to the enhanced safety through generation and use in situ (Table 2, entries 2 and 4).

It was noted that the chromatographic purification of α-diazoketones 8 and 11–13, synthesized by the telescoped TfN₃ flow methodology, afforded cleaner isolated products than those obtained from chromatographic purification of the crude products from the diazoethane acylation route; in particular, isolated α-diazoketone 8 was afforded in significantly improved purity than from the diazoethane acylation route (Figure 2).

With downstream processes in mind, ease of purification is an important benefit. Byproducts may prove to be detrimental to a transition-metal-catalyzed transformation in a telescoped process; the telescoped diazo-transfer process with trifly azide (22) furnished the crude α-diazoketones with minimal byproducts. The ¹H NMR spectra of the crude effluent, before being passed through the in-line silica gel plug, indicated the presence of just the α-diazoketone and DBU salts (which are removed by passage through a silica gel plug) with no other substantive byproducts.

Notably the telescoped generation of trifly azide and debenzyolative diazo transfer can be effected in toluene in place of dichloromethane, affording α-diazoketone 11 in 68% yield after chromatography, with just a minor decrease in yield relative to that in the chlorinated solvent (80%) (Scheme 8). Both toluene and dichloromethane are compatible with the downstream copper-mediated transformations. In addition to the advantage of using a more environmentally friendly solvent, there is also a very significant safety benefit, as the risk of formation of diazidomethane during the formation of the trifly azide is completely eliminated. For all of the processes described herein, the aqueous sodium azide solution and dichloromethane are typically in contact for less than 2 h; there are no reported instances of diazidomethane forming at room temperature in this time frame and there are multiple examples in the literature of sodium azide and dichloromethane being safely used together under similar conditions.

An in situ IR study was also undertaken, which supported this assertion (see the SI).

An important difference between the telescoped generation of trifly azide (22) and our previously reported method for mesyl azide generation in flow is that the liquid–liquid separation, to remove the aqueous stream, is carried out prior to the diazo-transfer step. This change was made as, in contrast to the homogeneous aqueous acetoniirle medium used for mesyl azide generation, a biphasic system (CH₂Cl₂/toluene/water) might lead to inefficient mixing between the reagents during the diazo-transfer step. The aqueous waste from the liquid–liquid separator can also be safely destroyed in a
Figure 2. Comparison of the $^1$H NMR spectra of $\alpha$-diazoketone 8 recorded after chromatography following synthesis in batch with diazoethane (A) and following synthesis with the telescoped TfN$_3$ methodology in flow (B). Spectra recorded in CDCl$_3$ at 400 MHz (showing residual CHCl$_3$ signal at $\delta^H$ 7.26).

Scheme 10. Synthesis of $\alpha$-Diazolactam 29 via Telescoped in Situ Generation of Triflyl Azide (22) and Deacylative Diazo Transfer

Figure 3. Flowchart for the telescoped generation of TfN$_3$ 22 and diazo transfer to diketone 19 in flow including the in-line removal of byproducts; required process inputs and desired output are shown in green; process byproducts are shown in orange; steps involving separation of byproducts are shown in blue; components of the process without user handling are shown in red.
continuous manner (see the SI for experimental details), based on the literature method.\textsuperscript{77}

The telescoped triflyl azide generation and debenzoylative diazo-transfer methodology affords a vastly improved safety profile relative to use of diazoalkane acylation, particularly when toluene is employed as the reaction solvent. Isolation and handling of hazardous diazoalkanes and nitrosoureas were avoided, while the organic azide was synthesized in a safe continuous manner without isolation or handling. Furthermore, the diazoethane acylation approach, in terms of overall yield, offers only marginally better results than the telescoped TfN\textsubscript{3} flow process; for example, synthesis of α-diazoketone 11 (Figure 1): 58% yield for diazoethane acylation (over two steps: carboxylic acid → acyl halide → α-diazoketone) versus 50% for debenzoylative diazo transfer (over three steps: carboxylic acid → acyl benzotriazole → 1,3-diketone → α-diazoketone).

The versatility of this telescoped process was further demonstrated by preparation of α-diazolactam 29 from the activated lactam 28, utilizing a decarboxylative diazo-transfer strategy,\textsuperscript{83,84} demonstrating that this approach can be generalized beyond debenzoylation (Scheme 10). In this instance, the triflyl azide was generated in toluene while the reagent solution was in dichloromethane indicating the process remains efficient in a mixed solvent system.

**Telescoped Aromatic Additions of α-Diazoketones.**

With the viability of our continuous flow strategy for generation and in situ use of triflyl azide (22) for debenzoylative diazo transfer leading to a range of α-diazocarbonyl compounds established, our attention turned to telescoping this process with copper-mediated asymmetric transformations, with an initial focus on intramolecular aromatic addition.

Generation of triflyl azide (22) and subsequent debenzoylative diazo-transfer reactions in flow provided a crude reaction effluent in a solvent suitable to use in a downstream copper-catalyzed aromatic addition (see Figure 3 for an overview of the overall process). Furthermore, excess sodium azide and any triflic acid were readily removed in the aqueous layer prior to diazo transfer, and subsequently, the organic effluent from the diazo transfer was readily purged of both DBU (or, most likely, its salt 30, Figure 3) and the sulfonyl benzamide byproduct by passing through a silica gel plug. The sulfonyl benzamide byproduct and DBU, each, potentially coordinate to the copper catalyst downstream, hindering the transition-metal-catalyzed aromatic additions, and therefore, their removal prior to flowing into the immobilized catalyst bed was critical for successful transition-metal-catalyzed transformation. Indeed, we have established experimentally that residual DBU is not compatible with the immobilized copper catalyst\textsuperscript{9}, as passing a diazo-transfer reaction solution containing DBU and its salts through the IPB catalyst\textsuperscript{9} (by omitting prior passage through silica gel) was found to lead to high levels of copper leaching—that is indicated by a dramatic change of color (green to white) occurring with concomitant loss of catalytic activity.

Evidently, the silica gel column has a finite capacity to retain the polar byproducts; accordingly, the volume of the solution of α-diazoketone passed over the immobilized copper catalyst\textsuperscript{9} was adjusted to avoid elution of any of the unwanted polar components.

Two telescoped processes comprising triflyl azide generation, debenzoylative diazo transfer, and aromatic addition were investigated, furnishing enantioenriched azulenone 31 and the PTAD adduct 10 derived from azulenone 32 (Scheme 11). In both transformations, the triflyl azide (22) prepared in flow was passed over KOH pellets in a round-bottomed flask as a reservoir and then pumped forward to effect debenzoylative diazo transfer with either 1,3-diketone 18 or 19.\textsuperscript{85}

The diazo-transfer effluent was also collected over KOH pellets, and an appropriate portion of this reaction solution,
containing the α-diazoketone 8 or 11, was pumped forward to undergo aromatic addition, ensuring the capacity of the silica gel column to retain the polar byproducts, especially the sulfonyl benzamide salts 30, is not exceeded and thereby avoiding leaching of the copper catalyst (vide supra). Following passage through silica gel, the stream containing α-diazoketone 8 or 11 was directly passed through a packed bed reactor containing IPB catalyst 9 (10 mol %). The aromatic addition of α-diazoketone 11 was performed at 45 °C, while the aromatic addition of α-diazoketone 8 was performed at room temperature.

The process afforded azulenone 31 in 50% yield after chromatography (over the two steps from the 1,3-diketone precursor 19). Rather than attempt to isolate and purify the labile azulenone 32, the reactor effluent containing 32 was collected into a flask containing PTAD in dichloromethane to transform it to the stable cycloadduct 10 prior to isolation; once all the effluent was collected, the contents of the flask were stirred for 1 h at room temperature and the product cycloadduct 10 was isolated in 30% yield (over three steps from 1,3-diketone precursor 18).

Critically, the isolated products 31 and 10 were afforded with comparable enantiopurities (60 and 82% ee, cf. 61% ee and 83% ee) to those reported for the transformations carried out with IPB 9 in batch and flow but which were not telescoped, instead using preprepared α-diazoketone.14 These results were encouraging and demonstrated that the telescoped trifly azide generation and subsequent diazo-transfer reaction produced an effluent, that after treatment with silica gel and drying agent, was sufficiently clean and anhydrous to undergo downstream transition metal-catalyzed transformations with no noticeable impact on enantioselection. While the yields were slightly lower than those achieved with pure α-diazoketones, the benefit of achieving these enantioselective transformations without isolating or handling either the trifly azide (22) or the α-diazoketone offsets this. These results demonstrate that the synthetic power of enantioselective transition-metal-catalyzed transformations of α-diazoketones can be achieved without handling either the hazardous precursor sulfonyl azide or the α-diazoketone and that the solution of the α-diazoketone generated in flow is sufficiently clean to flow directly into an immobilized copper catalyst without undermining the enantioselectivity.

It was notable that no signals associated with DBU or DBU salt 30 were observed in the 1H NMR spectra of the concentrated crude reaction effluents, indicating that, at least on the scale investigated, the silica gel column had successfully removed these byproducts. Despite employing KOH pellets as a drying agent, 2,3-diketone 34 (Scheme 12) was also afforded as a side product during the aromatic addition of α-diazoketone 11, and was clearly observed in the 1H NMR spectrum of the crude product mixture and was isolated after chromatography in 19% yield as a yellow oil.

Use of KOH pellets as a drying agent was undertaken to combat the impact of residual water in the reaction stream as it

![Scheme 12](https://pubs.acs.org/doi/10.1021/acs.joc.1c01310)
passes on to the immobilized copper catalyst. Although the liquid–liquid separator used following the upstream generation of triflyl azide successfully partitions the organic and aqueous phases, the organic layer is not anhydrous at this point. In order to test the effect that the water content of dichloromethane has on aromatic addition, a homogeneous Cu(PF6)−

Scheme 13. Synthesis of α-Diazoketone 36 with the Telescoped Flow Synthesis Using in Situ Generated Triflyl Azide

passes on to the immobilized copper catalyst. Although the liquid–liquid separator used following the upstream generation of triflyl azide successfully partitions the organic and aqueous phases, the organic layer is not anhydrous at this point. In order to test the effect that the water content of dichloromethane has on aromatic addition, a homogeneous Cu(PF6)−

Scheme 14. Synthesis of α-Diazo-β-ketonitrile 38 via a Telescoped Flow Synthesis Using in Situ Generated Triflyl Azide (22)

Furthermore, the effluent from the diazo-transfer stream was collected over KOH pellets before being pumped forward to undergo downstream aromatic additions. During the phase separation in the liquid–liquid separator, a small volume of dichloromethane remains after the triflyl azide separation has been undertaken and the solution progressed downstream to the diazo transfer. To check the efficiency with which the hazardous triflyl azide (22) was progressed through (Scheme 11), quantification of the amount of triflyl azide that remains in the residual dichloromethane phase in the separator was undertaken and estimated as approximately 2% of the total generated; this was readily quenched by addition of sodium acetylacetonate (6).

Telescoped Regitz-Type Diazotransfer in Flow. While the debenzylation of the diazo transfer using triflyl azide generated in flow proved very successful, generalizing this approach to standard Regitz diazo transfer was investigated to broaden the synthetic scope and specifically to enable telescoping with a C−H insertion process (vide infra). Accordingly, Regitz-type diazo transfer to form the novel α-diazo-β-ketonitrile 36 was achieved in an excellent yield of 94% (Scheme 13); in this instance, triethylamine was sufficiently basic to deprotonate β-hydroxyenone 35. The residence times, reagent ratios, and temperatures were consistent with the previously performed telescoped transformations. In the absence of an alkyl substituent at the α-carbon of the β-hydroxyenone, the reaction mechanism was seen to proceed entirely through Regitz diazo transfer, with no evidence for competing debenzylation. This result supports the extensive evidence reported by Regitz, Taber and others that the debenzylation pathway is only observed when the α-carbon possesses an alkyl substituent.

Diazotransfer to a β-Ketonitrile and α-Cyanoacetamides. Having demonstrated efficient synthesis of α-diazoketones via the in situ generation and use of triflyl
azide in flow, extension to a broader range of $\alpha$-diazocarbonyl compounds was undertaken to expand the scope of this approach with a particular focus on nitrile derivatives which can be challenging to access in certain instances. Accordingly, Regitz-type diazo transfer employing our telescoped triflyl azide generation and diazo-transfer methodology proved successful when employing $\beta$-ketonitrile 37 as the substrate, affording the desired $\alpha$-diazoo-$\beta$-ketonitrile 38 in 85% yield (Scheme 14); this outcome is comparable with the yields for $\alpha$-diazoo-$\beta$-ketonitriles under batch conditions reported by Charette, who had also utilized TN$_3$, 22,76 and with the yields obtained when imidazole-1-sulfonyl azide hydrochloride was used.94,95 It has also been demonstrated that acylation of diazoacetonitrile can afford $\alpha$-diazoo-$\beta$-ketonitriles;76 however, this reagent poses its own safety challenges.77 Interestingly, a debenzyloative diazo-transfer approach to 38 had proved unsuccessful, with the benzoylated starting material recovered essentially quantitatively.

Following the successful application of our telescoped triflyl azide generation and diazo-transfer methodology to a Regitz-type diazo transfer, for synthesis of $\alpha$-diazoo-$\beta$-ketonitrile 38, our attention was attracted to its potential for preparation of $\alpha$-cyano-$\alpha$-diazocacetamides. The reported synthesis of these $\alpha$-diazocarbonyl compounds, by Xu,71 required the use of triflyl azide (22) (Scheme 15), and therefore, these substrates appeared to be clear candidates for preparation via our telescoped flow procedures, without storage or handling of triflyl azide (22).

**Scheme 15. Synthesis Route to $\alpha$-Cyano-$\alpha$-diazaacetamides Reported by Xu**

$$\begin{align*}
\text{R} & \equiv \text{R'} \\
\text{N} & \equiv \text{CN} \\
\text{TN}_3 & \equiv \text{NE}_3
\end{align*}$$

The $\alpha$-cyanoacetamides 47–54 were synthesized by the route described by Xu (Scheme 16).71 A range of substituted benzaldehydes were transformed to secondary benzyl amines 39–46 by reductive amination with tert-butylamine or benzylicamine. These amines were then converted to amides in a DMAP-mediated coupling reaction with cyanoacetic acid. Compounds 47–54 were prepared on a synthetically useful scale (2–10 g) and were afforded as pure solids, usually upon recrystallization from ethanol, and were stable on storage at room temperature.

A modified version of the method reported by Xu,71 with triflyl azide (22) and using triethylamine as base, was utilized for synthesis of $\alpha$-cyano-$\alpha$-diazaacetamides 55–62 in batch (Table 4), as a means of comparing the outcome of their preparation via our telescoped continuous process. As part of this work, the potential viability of tosyl azide (TsN$_3$) and DBU, and also $p$-acetamidobenzensulfonil azide ($p$-ABSA) and triethylamine, were assessed for the diazo transfer to $\alpha$-cyanoacetamide 47, but without success. This outcome highlights the importance of developing a safe method for the generation and use of triflyl azide for diazo transfers which cannot be readily effected using less reactive sulfonil azides, although Xu had reported a single example of diazo transfer to an $\alpha$-cyanooacetamide using $p$-ABSA and DBU.98

The $^1$H NMR spectra of the crude reaction mixtures following concentration were relatively clean in all cases, and the $\alpha$-cyano-$\alpha$-diazaacetamides 55–62 were isolated after chromatography in yields ranging from moderate to excellent as yellow solids in most cases. These compounds were relatively stable and could be stored for extended periods in a freezer without any evidence of deterioration. Using this protocol, $\alpha$-cyano-$\alpha$-diazaacetamides can be readily accessed in multigram quantities, with the primary limitation being the scale of triflyl azide (22) handled.

Our telescoped preparation of triflyl azide (22) followed by Regitz diazo transfer was then applied to generate the $\alpha$-cyano-$\alpha$-diazaacetamides in flow (Table 4). Once again, the organic effluent from the in-line liquid–liquid separator was collected in a flask containing potassium hydroxide pellets before being immediately pumped forward to the diazo-transfer step.

In practice, synthetically useful amounts (3.0 mmol) of the $\alpha$-cyano-$\alpha$-diazaacetamides were prepared and purification by column chromatography was employed to ensure complete removal of the byproducts. Excellent yields were achieved across the series. Furthermore, the quality of the products isolated was comparable in flow or batch. It was notable that the yields for the $\alpha$-cyano-$\alpha$-diazaacetamides were more uniform in flow, across the series investigated, than the yields obtained in batch (Table 4 cf. Table 3), presumably due to enhanced control of reagent mixing and temperature.

Introduction of an in-line silica gel plug was undertaken with a view to telescoping the diazo transfer with subsequent transition-metal-catalyzed transformations by removal of the triethylamine salts in-line at smaller scales (approximately 1 mmol). Evidently, the volume of silica gel used in the plug must be appropriate to the scale of the reaction to avoid leaching of the polar byproducts—typically, in this work the reactions were conducted at a 1 mmol scale and using a 100 mm × 10 mm internal diameter glass column of silica gel. Notably, synthesis of gram quantities of $\alpha$-cyano-$\alpha$-diazaacetamides using this methodology in flow does not require inclusion of the silica gel column as chromatographic purification affords the products in analytically pure form, with or without the silica gel plug in a flow system.

While triflyl azide (22) is the most common choice of diazo-transfer reagent for synthesizing $\alpha$-cyano-$\alpha$-diazaacetamides, Reisman has reported using imidazole-1-sulfonil azide hydrochloride as an alternative in batch,95 although the reaction times reported are much longer (24 h vs approximately 4 h) and marginally lower yields were reported in comparison to yields obtained for the telescoped flow process in this work. Most importantly, however, as mentioned earlier, use of triflyl azide in flow.
azide (22) in flow offers clear safety advantages relative to its generation and use in batch.

**Telescoped C–H Insertion.** Earlier work by our team has demonstrated excellent enantiocontrol in intramolecular C–H insertions with α-diazo-β-oxosulfones;9,13 the generation and use of triaryl azide in flow for diazo transfer for the first time the possibility of telescoping the synthesis of α-diazo-β-oxosulfones with the copper-catalyzed C–H insertion leading to thiopyran S,S-dioxides. Key to this is the potential to prepare the α-diazo-β-oxosulfones in a solvent medium which is compatible with the catalyst and sufficiently clean to avoid catalyst poisoning or deterioration. Given its successful use for enantioselective intramolecular Buchner reactions in batch and using continuous flow processing,14 investigation of the use of IPB copper–bis(oxazoline) catalyst 9 in the copper-catalyzed desymmetrization of α-diazo-β-oxosulfone 63 was investigated.13 Use of the immobilized catalyst 9, in this instance, was key to a fully telescoped process involving triaryl azide generation, diazo transfer and direct C–H insertion reaction of α-diazo-β-oxosulfone 63 in continuous flow.

A number of heterogeneous batch reactions were initially conducted to support development of the final continuous process, as shown in Table 5. These reactions investigated whether the IPB copper–bis(oxazoline) catalyst 9 would afford efficient C–H insertion of α-diazo-β-oxosulfone 63, as observed upon homogeneous copper-catalyzed batch reactions,13 prior to attempting a telescoped diazo-transfer reaction and C–H insertion step in flow. To examine results of a homogeneous versus heterogeneous copper-catalyzed C–H insertion during this investigation, a homogeneous reaction was also undertaken for comparison using Cu(CH3CN)4PF6 (5 mol %) and the analogous (4R)-Ph bis(oxazoline) ligand 64 (6 mol %), in dichloromethane at reflux (Table 5, entry 5).

### Table 3. Synthesis of α-Diazo-α-cyanoacetamides 55–62 in Batch with Triaryl Azide (22)

| entry | substrate | diazo | R¹ | R² | yield (%) |
|-------|-----------|-------|-----|-----|-----------|
| 1     | 47        | 55    | H   |      | 66        |
| 2     | 48        | 56    | 4-Cl| t-Bu| 72        |
| 3     | 49        | 57    | H   | t-Bu| 65        |
| 4     | 50        | 58    | 4-F | t-Bu| 83        |
| 5     | 51        | 59    | 4-Me| t-Bu| 90        |
| 6     | 52        | 60    | 4-Br| t-Bu| 58        |
| 7     | 53        | 61    | 3,5-dimethyl | t-Bu| 46        |
| 8     | 54        | 62    | 4-pyridyl | t-Bu|           |

*a*Isolated after flash chromatography.

### Table 4. Synthesis of α-Cyano-α-diazoacetamides with the Telescoped Flow Synthesis Using in Situ Generated Triaryl Azide (22)

| entry | substrate | diazo | R¹ | R² | yield (%) |
|-------|-----------|-------|-----|-----|-----------|
| 1     | 47        | 55    | H   |      | 66        |
| 2     | 48        | 56    | 4-Cl| t-Bu| 65        |
| 3     | 49        | 57    | H   | t-Bu| 65        |
| 4     | 50        | 58    | 4-F | t-Bu| 83        |
| 5     | 51        | 59    | 4-Me| t-Bu| 90        |
| 6     | 52        | 60    | 4-Br| t-Bu| 58        |
| 7     | 53        | 61    | 3,5-dimethyl | t-Bu| 46        |
| 8     | 54        | 62    | 4-pyridyl | t-Bu|           |

*a*Isolated after flash chromatography.
Reactions using IPB copper catalyst \(9\) at 5 and 10 mol % (5 mol % fresh catalyst and 5 mol % of reused catalyst) loadings in dichloromethane at reflux did not achieve complete conversion of 63; the heterogeneous reaction was considerably slower than the homogeneous reaction, which was complete after 4 h (Table 5, entry 1 cf. entry 5).

After reflux for 24 h at a 10 mol % loading of \(9\) (Table 5, entry 2), 83% conversion was observed in the \(^1\)H NMR spectrum of the crude reaction mixture which resulted in a yield of 59% for 65 with 92% ee after column chromatography. The decrease in enantioselectivity from 97% ee to 92% ee observed, upon immobilization of the ligand, when using the IPB copper catalyst \(9\) is relatively modest and is in line with that observed for aromatic addition.\(^1\) As expected, the major enantiomer of 65 isolated from the use of the IPB (4S)-Ph bis(oxazoline) copper catalyst \(9\) was the \(1R,4aR,8aS\) enantiomer, the opposite enantiomer observed to that isolated from the homogeneous reaction when using the (4R)-Ph bis(oxazoline) ligand 64. This result highlights that very similar ligand–substrate interactions occur with the heterogeneous IPB copper catalyst, compared to the homogeneous copper-catalyzed reaction.

In an attempt to achieve 100% conversion of the \(\alpha\)-diazoo-\(\beta\)-oxosulfone 63, 15 mol % of \(9\) was used (5 mol % fresh catalyst and 10 mol % reused catalyst) with the reaction mixture heated under reflux for 48 h (Table 5, entry 3); however, only 78% conversion was achieved, with a 60% yield of thiopyran 65, while retaining 93% ee in the insertion product. An interesting point to note is that the regio- and diastereoselectivity of the reaction appear unaffected by use of the IPB copper catalyst \(9\); in common with similar homogeneously catalyzed reactions, 65 was found to be the major product.\(^1\)

Although maintaining a high level of stereoselectivity, achieving reaction completion in dichloromethane under reflux was challenging with the IPB copper catalyst \(9\). In order to facilitate the transition of the copper-catalyzed desymmetrization process of \(\alpha\)-diazoo-\(\beta\)-oxosulfone 63 to a continuous flow platform, the reaction would ideally reach completion in less than an hour to avoid requiring impractically low flow rates that would correspond to excessively long residence times. Accordingly, conducting the IPB copper-catalyzed C–H insertion of 63 in toluene, a higher boiling (bp 111 °C) and “greener” solvent compared to dichloromethane (bp 40 °C) was investigated with a view to reducing the reaction time.

Table 5. Heterogeneous Copper-Catalyzed C–H Insertion of \(\alpha\)-Diazoo-\(\beta\)-oxosulfone 63 in Batch

| Entry | Catalyst Loading \(9\) | Catalyst Run | Solvent | Time (h) | Conversion (%) | Yield (%) | % ee⁴ |
|-------|------------------------|--------------|---------|----------|---------------|-----------|-------|
| 1     | 5 mol%                 | 1<sup>e</sup> | CH₂Cl₂  | 24       | –60          | –         | –     |
| 2     | 10 mol%<sup>′</sup>     | 2<sup>nd</sup> | CH₂Cl₂  | 24       | –83          | 59        | 92<sup>Ⅲ</sup> |
| 3     | 15 mol%<sup>′</sup>     | 3<sup>rd</sup> | CH₂Cl₂  | 48       | –78          | 60        | 93<sup>Ⅳ</sup> |
| 4     | 10 mol%                | 1<sup>e</sup> | toluene | 0.5      | 100          | 57        | 88<sup>Ⅳ</sup> |
| 5<sup>ⅰ</sup> | Cu(CH₃CN)₄PF₆ | n/a | CH₂Cl₂ | 4 | 100 | 73 | 97<sup>ⅳ</sup> |

<sup>ⅰ</sup> Compound \(9\) was reused multiple times with addition of fresh catalyst (entries 1–3), collected by filtration once the crude reaction mixture was cooled to room temperature, agitated in fresh dichloromethane for 2 h, collected by filtration, and air-dried overnight. <sup>Ⅲ</sup> Reaction completion was determined by IR spectroscopic analysis upon disappearance of the diazo stretch for 63. <sup>Ⅳ</sup> Conversion was calculated on the basis of comparison of the integrations for the C(1)H doublet of doublets at δ<sub>H</sub> 3.75 (1H, J 4.7, 3.1 Hz) for 65 and the methyl singlet at δ<sub>H</sub> 3.88 (3H) for 63. <sup>Ⅵ</sup> Yields after column chromatography. <sup>Ⅶ</sup> The enantiopurity was measured by chiral-phase HPLC analysis (for full details, see the SI). <sup>ⅳ</sup> Fresh 9 was used to make up the difference in polymer catalyst mol % from the previous run. <sup>ⅲ</sup> Yield in parentheses was calculated on the basis of the percent conversion from the \(^1\)H NMR spectrum of the crude reaction material. <sup>ⅲ</sup> The major enantiomer has a \(1R,4aR,8aS\) configuration. <sup>ⅳ</sup> Homogeneous batch reaction. <sup>ⅳ</sup> Cu(CH₃CN)₄PF₆ (5 mol %) and (4R)-Ph BOX ligand 64 (6 mol %) used. <sup>ⅳ</sup> The major enantiomer has a \(1S,4aS,8aR\) configuration.
A heterogeneous reaction of \( \alpha \)-diazo-\( \beta \)-oxosulfone \( 63 \) was conducted using toluene under reflux with a fresh sample (10 mol %) of \( 9 \) in a manner similar to that employed for the other entries in Table 5, other than the change of solvent. The reaction was observed to occur rapidly (30 min) at the elevated temperature of 111 °C; however, some additional impurity signals were noticed in the \( ^1 \)H NMR spectrum of the crude product mixture, albeit with \( 65 \) still observed as the major product. Gratifyingly, \( 65 \) was isolated with a 57% yield and 88% ee after column chromatography. Both the yield and the enantioselectivity of \( 65 \) were reduced somewhat in comparison to those seen for the dichloromethane reactions using \( 9 \) and for the homogeneous reaction (Table 5, entries 1−5), however, with clear advantages in terms of reaction time and efficiency.

On the basis of these encouraging preliminary results using the IPB copper catalyst \( 9 \) in batch, the desymmetrization reaction was transferred to the three-step telescoped flow process. Initially, focusing on the diazo-transfer step, the synthesis of \( 63 \) was undertaken in flow in toluene via Regitz-type diazo transfer following triethyl azide formation (Scheme 17), with 80% yield of \( \alpha \)-diazoester \( 63 \) obtained after column chromatography, which was comparable to the batch reaction using the diazo-transfer agent \( p \)-ABSA. Thus, the triethyl azide flow methodology is also very effective for diazo transfer to \( \alpha \)-sulfonyl esters.

For the telescoped three-step continuous process, including C−H insertion, in situ prepared \( \alpha \)-diazo-\( \beta \)-oxosulfone \( 63 \) solution was pumped, first, through a glass column reactor packed with silica gel to remove polar reagents and byproducts (principally, DBU and DBU salts), followed subsequently by a glass column reactor packed with the IPB copper catalyst \( 9 \) (10 mol %) that was heated to 111 °C, where the final C−H insertion step occurred (Scheme 18).

The telescoped process resulted in the desymmetrized product \( 65 \) being isolated in 26% yield and 88% ee after column chromatography. Critically, this outcome showed that it is possible to utilize the reaction stream containing the \( \alpha \)-diazosulfone \( 63 \) directly in the copper-mediated C−H insertion without any deterioration in the enantiopurity of the desymmetrized product \( 65 \), albeit with a reduced yield. Thus, the telescoping is feasible not only with copper-mediated aromatic addition but also with the much more demanding C−H insertion into an unactivated bond. Although a lower yield was observed, the enantioselectivity observed is comparable to

Scheme 17. Synthesis of \( \alpha \)-Diazoketone 63 with the Telescoped Flow Synthesis Using In Situ Generated Triflyl Azide (22)

Scheme 18. Telescoped Process for the Synthesis and C−H Insertion of \( \alpha \)-Diazo-\( \beta \)-oxosulfone 63

https://doi.org/10.1021/acs.joc.1c01310
J. Org. Chem. 2021, 86, 13955−13982
that obtained when the heterogeneous batch reaction was conducted in toluene (Table 5, entry 4).

Thus, it appears the generation of triflyl azide (22) and telescoping this with the diazo transfer to form 63 proceeds efficiently; however, the outflow of the diazo transfer is a relatively complex solution containing a stoichiometric amount of DBU, triflyl sulfonamide and potentially other byproducts which could detrimentally impact on the IPB copper catalyst. Observation of enantioselective C−H insertion, albeit at a reduced efficiency compared to a typical homogeneous reaction,\(^{13}\) solely by passing the reaction mixture through silica gel, offers promise that this process can be further optimized in terms of yield, especially as the extent of the enantioselectivity was not detrimentally affected (88% ee). Notably, the synthesis of triflyl azide (22), the diazo transfer to 66, and the copper-mediated C−H insertion can be conducted in a single telescoped process without detrimental impact on the stereochromatic outcome and, in particular, the enantioselectivity of the thiopyran dioxide 65.

Previous literature reports generated or utilized TsN₃ in solvents which had detrimental effects on the yields of downstream transition-metal-catalyzed processes, such as NMP\(^{41}\) or MeCN.\(^{39}\) In addition to the high level of reactivity of TfN₃, one of the primary reasons for selecting TfN₃ as diazo-transfer reagent was due to the ability to generate the compound in a solvent (toluene or dichloromethane in this work) which was amenable for use in downstream transition-metal-catalyzed processes without requiring a solvent swap. Ultimately, the potential hazard of residual triflyl azide (22) in the reaction outflow was mitigated by two features: (1) in the development of the diazo transfer telescoped with triflyl azide formation, it was established using IR spectroscopy that no residual triflyl azide (22) was present in the reaction outflow, for the reagent ratio levels employed; (2) reaction monitoring of each the reaction effluents by IR spectroscopy prior to concentration showed no evidence of the characteristic azide stretch for triflyl azide (22), or indeed sodium azide. As summarized in Figure 5 the synthetic power of triflyl azide and the α-diazocarbonyl compounds has been effectively exploited, in tandem with immobilized copper catalysts, in transforming achiral starting materials to highly enantioenriched products while obviating the need to isolate, handle, or store these compounds.

**CONCLUSION**

While triflyl azide (22) is a very powerful reagent for diazo transfer, its use is limited by the hazards associated with its handling. Generation and use of triflyl azide in flow leads to efficient synthesis of a range of α-diazocarbonyl compounds, including α-diazoketones 8, 11−13, an α-diazolactam 29, α-cyano-α-diazocarbonyl compounds 55−62, an α-diazoo-β-ketonitrile 38, and an α-diazosulfonyl ester 63, via both Regitz-type diazo transfer and deacylative/debenzyolative diazo-transfer processes in excellent yields (70−96%) and offers versatility in the solvent employed, in addition to addressing the hazards associated with handling of this highly reactive sulfonil azide. Notably, triflyl azide (22) led to successful diazo transfer to form α-diazoacetamides 8 and 11−13 with substantially higher yields than achieved with tosyl azide in flow. Furthermore, using this continuous flow protocol the diazo substrates are generated in solvents that are compatible with downstream transition-metal-catalyzed processes, such as toluene and dichloromethane. Telescoping the generation of the triflyl azide (22) and diazo-transfer process with enantioselective copper-mediated intramolecular aromatic addition and C−H insertion processes demonstrates that the reaction stream of the α-diazocarbonyl compound can be obtained in sufficient purity to pass directly into the immobilized copper bis-(oxazoline) catalyst 9 without detrimentally impacting on the enantioselectivity observed. Thus, azulenones 31 and 32 (as its PTAD adduct 10) were obtained in 60% ee and 82% ee, in 50% and 30% yield respectively, with little or no decrease in enantioselectivity observed when the Buchner addition was telescoped with the diazo-transfer protocol. Furthermore, the desymmetrisation via copper-mediated C−H insertion to form the thiopyran S,S-dioxide proved successful in toluene, leading to the desymmetrized product in 88% ee, comparable with the enantioselectivity observed using the immobilized copper catalyst in a batch reaction.

**EXPERIMENTAL SECTION**

**General Procedures.** Solvents were distilled prior to use as follows: dichloromethane was distilled from calcium hydride when used for transformations of α-diazoketones, ethyl acetate was distilled from potassium carbonate, tetrahydrofuran was distilled from sodium benzophenone ketyl in a nitrogen atmosphere and hexane was distilled prior to use. All commercial reagents were used without further purification unless otherwise stated. Amines 39−46,\(^{33}\) sulfonyl 63,\(^{13}\) and pyrrolidinone 28,\(^{13}\) were prepared according to literature methods. Insoluble polymer bound (IBP) catalyst 9 was prepared from copper(1) hexafluorophosphate and 2,2′-(1,3-bis(4-vinylphenyl)propylene)dibis((4S)-4-phenyl-4,5-dihydro-2-oxazole) polymer as previously reported.\(^{14}\)

\(^{1}H\) (300 MHz) and \(^{13}C\) (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. \(^{1}H\) (400 MHz) and \(^{13}C\) (100.6 MHz) NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform (CDCl₃) unless otherwise stated, using tetramethylsilane (TMS). Chemical shifts (δₑ and δₛ) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz (Hz). \(^{31}P\) NMR spectra showed chemical shifts (δₚ) measured relative to hexafluorobenzene, which shows a single resonance at −163.0 ppm.

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Figure 5. Summary of process inputs and outputs.
Splitting patterns in $^1$H spectra are designated as s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), bt (broad triplet), q (quartet), qu (quinet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublets of doublets), td (triplet of doublets), ddt (doublet of triplets of doublets), AB (AB system), or (m) multiplet. $^{13}$C NMR spectra were calibrated using the solvent signal, i.e. CDCl$_3$: $\delta$ = 77.0 ppm, and multiplicities were assigned with the aid of DEPT experiments. Assignment of $^1$H signals was aided using 2D NMR including $^1$H−$^1$H COSY, HSQC and HMBC.

Infra-red spectra were measured using a Perkin−Elmer FTIR UATR2 spectrometer.

Organic phases were dried using magnesium sulfate or potassium hydroxide pellets. Flash column chromatography was carried out using Kieselgel silica plates (Merck 60 PF254). Visualization was achieved by UV (254 nm) light. Chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualization was achieved by UV (254 nm) light absorption.

Elemental analysis was carried out by Microanalysis Laboratory, National University of Ireland, Cork, using Exeter Analytical CE440 elemental analysers. Low-resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier ToFLC−MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent or on an Agilent 6530B Accurate Mass Q;TOF LC/MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent. High-resolution (precise) mass spectra (HRMS) were also recorded on a Waters V ion MS instrument (SAAO55 K) with Waters Acquity 1-class UPLC in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent and Leucine Enkcephalin as reference solution. Samples were prepared for either LRMS or HRMS by employing acetonitrile as solvent and are accurate to within 5 ppm.

Melt points were obtained using a Unimelt Thomas-Hoover Capillary melting point apparatus and are uncorrected. Enantiopurity of chiral compounds was determined by chiral stationary phase high-performance liquid chromatography (HPLC) performed on a Chiralcel OD-H or Lux Amylose-1 column. HPLC analysis was performed on a Waters alliance 2690 separations module. All chiral columns were purchased from Daicel Chemical Industries Limited or Phenomenex. Optical rotations were measured at 589 nm in a 10 cm cell on a PerkinElmer 141 polarimeter or on a Rudolph Autopol V Plus polarimeter; concentrations ([c]) are expressed in g/100 mL, and the specfic rotation of a compound and is expressed in units of 10$^{-1}$ deg cm$^2$ g$^{-1}$.

All continuous processes were performed using a flow chemistry system consisting of four HPLC pumps and up to four temperature-controlled tubular reactors (a glass reactor manifold containing a temperature controlled glass column) and a flow chemistry system consisting of three peristaltic pumps. To prepare the reactor for operation pumps were purged with the solvent to be used in the reaction prior to use. All reaction tubing, coils, inlets and connections were also purged thoroughly in a similar manner. All pumps were primed using appropriate solvents and pump backwash reservoirs were filled. The solvent that was to be used was flushed through all injectors and reactors. Pumps were run at reaction flow rates to check for stability, in both reagent and solvent lines, before committing reagents. Reactors that were to be used were then heated to the desired temperatures, using the flow chemistry platform, to check system pressurization. General specifications of flow systems used: *Material of tubing:* PFA; *Diameter of tubing:* 1 mm; *Working flow rates:* 0.05 mL/min − 9.99 mL/min; *Tubular reactor working volume:* 10 mL; *Temperature range:* −70 to +250 °C.

**Preparation of 1,3-Diketones. General Procedure for Preparation of Acyl Benzotriazoles.**

Thionyl chloride (1.15 equiv) was added in one portion to a stirring solution of (1H)−benzotriazole (4.25 equiv) in dichloromethane. The resulting yellow solution was stirred at room temperature for 30 min, after which carbonyl acid (1 equiv) was added in one portion. A white suspension formed following the addition, which was stirred at room temperature for 2 h. The suspension was filtered by gravity filtration, and the white solid collected was washed with dichloromethane ($2 \times 30$ mL). The combined organic washings and filtrate were collected, dried, and concentrated under reduced pressure to afford the crude acylbenzotriazole.

This compound was prepared according to the general procedure using thionyl chloride (1.0 mL, 13.0 mmol), (1H)−benzotriazole (5.80 g, 48.7 mmol), 3-methyl-3-phenylbutanoic acid (2.03 g, 11.4 mmol) and dichloromethane (75 mL). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent which afforded acylbenzotriazole as a colorless oil (2.39 g, 75%). $\nu_{max}/cm^{-1}$ (ATR): 2966, 1739, 1596, 1484, 1450, 1365. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.21 (d, 1H, $J$ = 8.3 Hz, ArH), 8.08 (d, 1H, $J$ = 8.2 Hz, ArH), 7.69−7.55 (m, 1H, ArH), 7.51−7.41 (m, 3H, ArH), 7.33−7.26 (m, 2H, ArH), 7.21−7.13 (m, 1H, ArH), 3.82 (s, 2H, C(2′)CH$_2$), 1.60 (s, 6H, C(3′)(CH$_3$)$_2$); $^{13}$C{1H} NMR (CDCl$_3$, 100.6 MHz): $\delta$ = 170.4 (C), 147.6 (C), 146.2 (C), 131.0 (C), 130.2 (C), 128.3 (CH), 126.3 (CH), 125.5 (CH), 120.1 (CH), 114.6 (CH), 47.7 (CH$_2$), 38.0 (C), 29.2 (CH$_2$). HRMS (ESI) m/z: [M + H]$^+$ Calc for C$_7$H$_8$N$_3$O, 139.0914; Found 139.0875.

 This compound was prepared according to the general procedure using thionyl chloride (2.30 mL, 30.0 mmol), (1H)-benzotriazole (14.30 g, 120.0 mmol), 3-methyl-3′-(3′,4′,5′-trimethylphenyl)butanoic acid (6.59 g, 30.0 mmol) and dichloromethane (100 mL). The crude acyl benzotriazole was isolated as a brown oil (8.31 g, 86%− due to the high viscosity of the sample (and consequent difficulty with solvent removal in vacuo), it contained residual dichloromethane ($\delta$=5.30 ppm)—estimated corrected yield 64% and carried forward without chromatographic purification. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.23 (d, 1H, $J$ = 8.3 Hz, ArH), 8.08 (d, 1H, $J$ = 8.3 Hz, ArH), 7.63−7.54 (m, 2H, ArH), 7.51−7.41 (m, 2H, ArH), 7.07 (s, 2H, C(2′′)H$_2$) and C(6′′)H$_2$), 7.38 (s, 2H, C(2′′)CH$_2$), 2.23 (s, 6H, C(3′)(CH$_3$)$_2$ and C(5′′)(CH$_3$)$_2$), 2.08 (s, 3H, C(4′′′′)(CH$_3$)), 1.56 (s, 6H, C(3′′′′)(CH$_3$)$_2$).

 This compound was prepared according to the general procedure using thionyl chloride (1.03 mL, 13.8 mmol), (1H)-benzotriazole (6.59 g, 55.36 mmol), 3-methyl-3′-(4′-chlorophenyl)butanoic acid (2.94 g, 13.48 mmol), and dichloromethane (75 mL). The crude acyl benzotriazole was isolated as a colorless oil (3.09 g, 71%) and carried forward without chromatographic purification. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.20 (d, 1H, $J$ = 8.3 Hz, ArH), 8.10 (d, 1H, $J$ = 8.3 Hz, ArH), 7.65−7.56 (m, 1H, ArH), 7.44−7.36 (m, 2H, ArH), 7.30−7.22 (m, 2H, ArH), 3.81 (s, 2H, C(2′′′′′)(CH$_3$)$_2$); $^{13}$C{1H} NMR (CDCl$_3$, 100.6 MHz): $\delta$ = 170.1 (C), 146.2 (C), 146.1 (C), 132.0 (C), 131.0 (C), 130.4 (CH), 128.4 (CH), 127.0 (CH), 126.2 (CH), 120.1 (CH), 114.5 (CH), 47.6 (CH$_2$), 37.6 (C), 29.3 (CH$_3$).
Lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M in THF, 17.7 mL, 17.7 mmol) was added to freshly distilled tetrahydrofuran (60 mL) and cooled to −80 °C (Bath temp). A tetrahydrofuran solution (10 mL) of propiophenone (2.2 mL, 16.8 mmol) was added slowly over 15 min. The reaction mixture was stirred at −80 °C for 1 h after which a tetrahydrofuran solution (15 mL) of 1′-(1H-benzo[d][1,2,3]triazol-1-yl)-3′-methyl-3′-phenylbutan-1′-one (4.68 g, 16.8 mmol) was added in one portion. The reaction mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was diluted with aqueous hydrochloric acid (3.2 M, 30 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The organic layers were combined, dried, and concentrated under reduced pressure.

The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent which afforded diketone 19 as a colorless oil (2.75 g, 56%) and fractionated by flash chromatography on silica gel with hexane/ethyl acetate (97:3) as eluent which afforded diketone 20 as a colorless oil (6.43 g, 85%).

This compound was prepared according to the procedure described for 19 from lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M in THF, 25.0 mL, 25.0 mmol), propiophenone (3.05 mL, 23.0 mmol), and 1′-(1H-benzo[d][1,2,3]triazol-1-yl)-3′-methyl-3′-(4′-chlorophenyl)butan-1′-one (7.22 g, 23.0 mmol) in THF (100 mL). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (97:3) as eluent which afforded diketone 21 as a colorless oil (8.47 g, 73%).

This compound was prepared according to the procedure described for 19 from lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M in THF, 17.7 mL, 17.7 mmol), propiophenone (1.02 mL, 7.70 mmol) and 1′-(1H-benzo[d][1,2,3]triazol-1-yl)-3′-methyl-3′-(4′-fluorophenyl)butan-1′-one (2.30 g, 7.70 mmol) in THF (75 mL). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (97:3) as eluent which afforded diketone 22 as a colorless oil (2.17 g, 62%).

This compound was prepared according to the procedure described for 19 from lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M in THF, 17.7 mL, 17.7 mmol), propiophenone (3.05 mL, 23.0 mmol), and 1′-(1H-benzo[d][1,2,3]triazol-1-yl)-3′-methyl-3′-(4′-fluorophenyl)butan-1′-one (7.22 g, 23.0 mmol) in THF (100 mL). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (97:3) as eluent which afforded diketone 24 as a colorless oil (3.41 g, 85%).
ArH), 7.48–7.39 (m, 2H, ArH), 7.30–7.20 (m, 4H, ArH), 7.19–7.11 (m, 1H, ArH), 3.94 [t, 1H, J = 6.8 Hz, C(2)H], 2.76 [AB, 2H, JAB = 14.0 Hz, H2, δ = 2.79, 2.74, C(4)H2], 1.83 (qd, 2H, J = 7.3, 7.2 Hz, CH2CH3), 1.40, 1.35 [2 × 2, 2 × 3H, C(5)(CH3)], 0.77 (t, 3H, J = 7.4 Hz, CH2CH3). 13C{1H} NMR (CDCl3, 100.6 MHz): δ 204.5 (C), 197.0 (C), 148.0 (C), 136.3 (C), 133.5 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 125.9 (CH), 125.5 (CH), 125.0 (CH), 121.1 (CH), 136.7 (CH2), 132.7 (CH), 131.9 (CH), 33.4 (CH3), 33.3 (CH3), 30.7 (CH2), 28.3 (CH3), 23.6 (CH3), 26.0 (CH3). HRMS (ESI) m/z: [M + H]+. Calculated for C24H23O2N, 395.1767. Found: 395.1750.

The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent which afforded diketone 25 as a colorless oil (1.77 g, 59%). 1H NMR (CDCl3, 400 MHz): 7.82–7.72 [m, 2H, ArH], 7.61–7.54 [m, 1H, ArH], 7.48–7.39 (m, 2H, ArH), 7.30–7.21 (m, 4H, ArH), 7.19–7.12 (m, 1H, ArH), 4.18 [t, 1H, J = 6.8 Hz, C(2)H], 2.77 [AB, 2H, JAB = 14.2 Hz, H2, δ = 2.80, 2.75, C(4)H2], 1.76–1.44 (m, 7H), 1.40, 1.34 [2 × 2, 2 × 3H, C(5)(CH3)], 1.20–0.90 (m, 20H, C). 13C{1H} NMR (CDCl3, 100.6 MHz): δ 204.5 (C), 197.0 (C), 148.0 (C), 136.3 (C), 133.5 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 125.9 (CH), 125.5 (CH), 125.0 (CH), 121.1 (CH), 136.7 (CH2), 132.7 (CH), 131.9 (CH), 33.4 (CH3), 33.3 (CH3), 30.7 (CH2), 28.3 (CH3), 23.6 (CH3), 26.0 (CH3). HRMS (ESI) m/z: [M + H]+. Calculated for C24H23O2N, 395.1767. Found: 395.1750.

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This compound was prepared according to the general procedure from N-([4-fluorobenzyl]-2-methylpropan-2-amine (42) (6.24 g, 34.0 mmol), 2-cyanoacetic acid (3.03 g, 36.0 mmol), N,N-dicyclohexylcarbodiimide (7.35 g, 36.0 mmol), and 4-dimethylaminopyridine (0.21 g, 1.73 mmol) in dichloromethane (60 mL). Colorless crystals (2.95 g, 69%). Mp: 160–161 °C. 1H NMR (CDCl3, 400 MHz): δ 6.93 (s, 1H, C(4′)H), 6.77 (s, 2H, C(2′)H and C(6′)H), 4.49 (s, 2H, NCH2), 3.43 (2H, CH2CN), 2.32 (2H, C(3′)CH3 and C(5′)CH3), 1.48 (s, 9H, C(CH2)3). 13C{1H} NMR (CDCl3, 100.6 MHz): δ 2260 (CN), 1659 (CO). 1H NMR (CDCl3, 400 MHz): δ 6.93 (s, 1H, C(4′)H), 6.77 (s, 2H, C(2′)H and C(6′)H), 4.49 (s, 2H, NCH2), 3.43 (2H, CH2CN), 2.32 (2H, C(3′)CH3 and C(5′)CH3), 1.48 (s, 9H, C(CH2)3). 13C{1H} NMR (CDCl3, 100.6 MHz): δ 163.0 (C), 139.0 (C), 137.3 (C), 129.4 (CH2), 122.9 (CH), 114.6 (C), 59.3 (C), 49.1 (CH2), 28.4 (CH3), 27.9 (CH2). HRMS (ESI) m/z: [M + H]+ Calcd for C7H5NO2 259.1805; Found 259.1802.

N-tert-Butyl-2-cyano-N-(4'-methyl)benzylacetamide (54).

This compound was prepared according to the general procedure from N-pyridin-4'-ylmethyl)-2-methylpropan-2-amine (46) (6.99 g, 42.6 mmol), N,N-dicyclohexylcarbodiimide (8.87 g, 43.0 mmol), cyanoacetic acid (3.66, 43.0 mmol), and 4-dimethylaminopyridine (0.24 g, 1.9 mmol) in dichloromethane (60 mL). The crude residue was not recrystallized but was washed with warm diethyl ether to afford pure acetamide 54 as a pale brown solid (8.09 g, 82%). Mp: 108–111 °C. νmax/cm\(^{-1}\) (ATR): 2977, 2256, 1660, 1602, 1432, 1362, 1191. HRMS (ESI) m/z: [M + H]⁺ Calcd for C14H16N2O 232.1444; Found 232.1440. Two sets of signals exist due to the presence of rotamers. Major rotamer (83%): 1H NMR (CDCl3, 400 MHz): δ 8.65 [d, 2H, J = 3.0 Hz, C(2)H and C(6)H], 7.17 [d, 2H, J = 5.7 Hz, C(3)H and C(5)H], 4.58 (s, 2H, CH2CN), 3.40 (s, 2H, CH2CN), 1.47 [s, 9H, C(CH2)3]. 13C{1H} NMR (CDCl3, 100.6 MHz): δ 162.8 (C), 150.7 (C), 147.0 (C), 120.5 (CH), 114.1 (C), 59.6 (C), 48.4 (CH2), 28.5 (CH3), 27.9 (CH3).

Minor rotamer (17%): 1H NMR (CDCl3, 400 MHz): δ 8.55 [d, 2H, J = 5.9 Hz, C(2)H and C(6)H], 7.47 [d, 2H, J = 5.8 Hz, C(3)H and C(5)H], 3.94 (s, 2H, CH2CN), 3.23 (s, 2H, CH2CN), 1.23 [s, 9H, C(CH2)3]. 13C{1H} NMR (CDCl3, 75.5 MHz) 166.7 (C), 150.0 (CH2), 124.9 (CH), 117.4 (C), 56.5 (C), 44.4 (CH3), 27.3 (CH3), 26.0 (CH2). Signal for C(1) not observed.

Synthesis of α-Diazo ketones via Debenzyolative Diazo Transfer. 3-Diazopentan-2,4-dione (23).
min−1). The reaction stream was passed through a back-pressure regulator (8 bar). The biphasic effluent was then separated by an inline liquid–liquid separator. The organic effluent (25 mL) was directly fed to another pump. The pump delivered the separated triethyl azide solution (25 mL, 0.17 mL min−1) to a T-piece where it met a solution of the relevant acceptor substrate (25 mL, 0.12 M, 1 equiv, [base] 0.128 M, 1.1 equiv, 0.17 mL min−1) which was then passed through a reactor coil (4 × 10 mL, rt, τ = 2 h) and subsequently through a glass column packed with silica gel (100 mm × 10 mm internal diameter) and then finally passed through a back pressure regulator (8 bar). The reactor effluent was analyzed by IR spectroscopy and concentrated under reduced pressure affording the crude α-diazoketone which was subsequently purified by flash chromatography on silica gel with hexane/ethyl acetate as eluent.

For the synthesis of compounds 55–62, the triethyl azide solution was collected over KOH prior to use in diazo transfer.

2-Diazo-5-methyl-5-(3',4',5'-trimethylphenyl)hexan-3-one (8).14

This compound was prepared according to the general flow procedure from 2,5-dimethyl-1-phenyl-5-(3',4',5'-trimethylphenyl)hexane-1,3-dione (18) and DBU (25 mL, 0.12 M, [DBU] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent affording α-diazoketone 8 as a yellow oil (0.558 g, 72%). νmax/cm−1 (ATR): 2967, 2066, 1625.1H NMR (CDCl3, 300 MHz): δ 7.30–7.26 [m, 4H, ArH2], 7.02–6.96 [m, 2H, 2 × ArH], 6.28 [2H, C(4)H2], 1.81 [s, 3H, C(1)H3], 1.46 [s, 6H, C(5)(CH3)2]. 13C{1H} NMR (CDCl3, 75.5 MHz): δ 192.5 (C), 131.8 (C), 128.2 (CH), 127.0 (CH), 63.6 (C), 50.3 (CH3), 38.0 (C), 29.1 (CH3), 8.1 (CH3).

2-Diazo-5-methyl-5-(4'-fluorophenyl)hexan-3-one (13).14

This compound was prepared according to the general flow procedure from a dichloromethane solution of 2,5-dimethyl-1-phenyl-5(4'-fluorophenyl)hexane-1,3-dione (21) and DBU (25 mL, 0.12 M, [DBU] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent affording α-diazoketone 13 as a yellow oil (0.491 g, 70%). νmax/cm−1 (ATR): 2967, 2066, 1625.1H NMR (CDCl3, 300 MHz): δ 7.33–7.28 [m, 2H, 2 × ArH], 7.02–6.96 [m, 2H, 2 × ArH], 6.28 [2H, C(4)H2], 1.81 [s, 3H, C(1)H3], 1.46 [s, 6H, C(5)(CH3)2]. 13C{1H} NMR (CDCl3, 75.5 MHz): δ 192.8 (C), 161.2 (C, d, JCF 244.2), 143.6 (C), 127.1 (CH, d, JCF 7.8), 114.8 (CH, d, JCF 20.9), 63.7 (C), 50.7 (CH3), 38.0 (C), 28.8 (CH3), 21.4 (CH3).

5-Diazo-2-methyl-2-phenylethanol-4-one (26).

This compound was prepared according to the general flow procedure from a dichloromethane solution of 2-ethyl-5-methyl-1,5-diphenylhexan-3-one (24) and DBU (25 mL, 0.12 M, [DBU] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (90:10) as eluent affording α-diazoketone 26 as a yellow oil (0.552 g, 80%). νmax/cm−1 (ATR): 2928, 2067, 1609.1H NMR (CDCl3, 300 MHz): δ 7.39–7.27 [m, 4H, ArH2], 7.24–7.15 [m, 1H, ArH], 6.27 [2H, C(3)(CH3)2], 2.22 [2H, J = 7.3 Hz, C(6)H2], 1.84 [6H, C(1)(CH3)2], 0.94 [4H, JCF 7.7 Hz, C(7)(CH3)2]. 13C{1H} NMR (CDCl3, 100 MHz): δ 192.4 (C), 147.9 (C), 128.2 (CH), 126.1 (CH), 125.6 (CH), 69.5 (C), 51.0 (CH3), 38.5 (C), 28.6 (CH3), 16.0 (CH3), 11.2 (CH3). HRMS (ESI) m/z: [M + Na]+. Calcd for C16H17N3O2Na 253.1311; Found 253.1312.

1-Cyclohexyl-2-diazo-5-methyl-5-phenylhexan-3-one (27).

This compound was prepared according to the general flow procedure from 2-cyclohexylmethyl-5-methyl-1-diphenylhexane-1,3-dione (25) and DBU (25 mL, 0.12 M, [DBU] 0.128 M), aqueous sodium azide (10 mL, 3.0 M) and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent affording α-diazoketone 27 as a yellow oil (0.812 g, 91%). νmax/cm−1 (ATR): 2922, 2060, 1627.1H NMR (CDCl3, 400 MHz): 7.39–7.27 [m, 4H, ArH2], 7.23–7.16 [m, 1H, C(4′)H], 6.29 [2H, C(4′)H2], 2.03 [2H, d, J = 7.1 Hz, C(2′)H2], 1.78–1.38 [m, 11H, contains singlet at 1.48 ppm for C(5)(CH3)2], 1.32–1.09 [m, 4H, 0.90–0.69 [2H, m, 1H, C(1′)H], 0.91–0.82 [6H, m, 1H, C(6′)H2], 1.84–1.75 [m, 1H, C(5′)H]. 13C{1H} NMR (CDCl3, 100 MHz) 192.6 (C), 147.8 (C), 128.2 (CH), 126.1 (CH), 125.6 (CH), 67.0 (C), 50.8 (CH3), 38.5 (C), 36.7 (CH3), 32.6 (CH3), 30.4 (CH3), 28.8 (CH3), 26.2 (CH3), 26.0 (CH3). HRMS (ESI) m/z: [M + Na]+. Calcd for C15H18N2O2Na 231.1937; Found 231.1940.

1-(4-Chlorophenyl)-3-diazopyrrolin-2-one (29).91

An aqueous solution of sodium azide (10 mL, 3.0 M, 1 equiv, 3.0 mL min−1) was pumped through a microcrimp T-piece where it met a
toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M, 1.67 equiv, 3.0 mL min⁻¹); the combined stream passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.2 mL min⁻¹ to give a residence time of 1 h. The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% v/v, 0.9 mL min⁻¹). The reaction stream was passed through a back-pressure regulator (8 bar). The biphasic effluent was then separated by an in-line liquid–liquid separator. The organic effluent (25 mL) was directly fed to another pump. The pump delivered the separated triethyl azide solution (25 mL, 2.0 mL min⁻¹) to a T-piece where it met a solution of ethyl-2-hydroxy-2-(4-chlorophenyl)pyrrolidin-3-yliden acetate (28) and DBU in dichloromethane (25 mL, 0.12 M, [DBU] 0.128 M, 1.1 equiv relative to 28, 2.0 mL min⁻¹) and was then passed through a reactor coil (4 × 10 mL, rt). When both reagent solutions had been charged, the combined flow rate was reduced to 0.5 mL min⁻¹ to give a residence time of 1 h, after which the reactor effluent subsequently passed through a back pressure regulator (8 bar). The reactor effluent was analyzed by IR spectroscopy and concentrated under reduced pressure to give crude product which was subsequently purified by chromatography on silica gel (treated by adding 1% weight of triethylamine to the dry silica prior to packing) using hexane:chloroform:ethanol (50:49:1) as eluent. The compound was observed in the 1H NMR spectrum of the crude product mixture in a ratio of 1:0.3 (30:34). The 2,3-diketone 34 was isolated after chromatography on silica gel with hexane/ethyl acetate as a yellow oil (0.039 g, 19%). ν_m (cm⁻¹) (film) 2967, 1713. 1H NMR (CDCl₃, 300 MHz): δ 7.37–7.25 (m, 4H, ArH), 7.22–7.15 (m, 1H, ArH), 3.09 [s, 2H, C(4)H₂], 1.98 [s, 3H, C(1)H₃], 1.45 [s, 6H, C(5)CH₃] ppm. HRMS (EI) m/z: [M + H⁺]⁺ Calc for C₁₀H₁₅N₁O₂: 199.1109; Found: 199.1107. The compound was also isolated during the aromatic addition reaction of α-diazoketone 11 as the side product: 5-Methyl-5-phenylhexane-2,3-dione (34) (88% yield). An aqueous solution of sodium azide (10 mL, 30 mmol, 3.0 M, 3.0 mL min⁻¹) was pumped through a micro mixer T-piece where it met a dichloromethane solution of triethyl azide (10 mL, 5 mmol, 0.5 M, 3.0 mL min⁻¹); the combined biphasic stream was passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.2 mL min⁻¹ to give a residence time of 1 h for triethyl azide generation. The reactor effluent for the first step passed through a T-piece where it met a stream of saturated aqueous sodium bicarbonate (0.1 mL min⁻¹). The combined stream was passed through a back pressure regulator (8 bar). The biphasic effluent was then separated by an in-line liquid–liquid separator and the dichloromethane effluent (25 mL), containing triethyl azide (22), was collected over KOH pellets. The separated dichloromethane triethyl azide solution (25 mL, 0.17 mL min⁻¹) was pumped to a T-piece where it met a dichloromethane solution of 2,5-dimethyl-1-phenyl-3,4,5-trimethylphenylhexane-1,3-dione (18) and DBU (25 mL, 3 mmol, 0.12 M, [DBU] 0.128 M, 0.17 mL min⁻¹) and the combined stream was then passed through a reactor coil (4 × 10 mL, rt, 120 min residence time). The diazo-transfer effluent (75 mL) was also collected over KOH pellets, and a 25 mL portion, containing the α-diazoketone 11, was pumped forward to undergo aromatic addition; this 25 mL solution was passed through a silica gel plug (glass column, 100 mm × 10 mm internal diameter, rt, 0.75 mL min⁻¹) to remove polar components. Immediately after eluting from the silica gel plug, the effluent was passed through a packed bed reactor containing IPB catalyst 9 (0.417 g, 10 mol % based on 19, glass column, 150 × 66 mm internal diameter, 0.75 mL min⁻¹, 45°C). The reactor effluent was analyzed by IR spectroscopy and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with hexane/ethyl acetate (95:5) as eluent, affording azulene 31 as a pale yellow oil (0.095 g, 50%, 60% ee). [α]_D²⁰ +13.86 (c 1.05, CHCl₃), ν_m (cm⁻¹) (ATR): 3042, 2926, 1747 (CO), 1715 (CO). 1H NMR (CDCl₃, 300 MHz): δ 6.43–6.23 (m, 3H, C(4)H₃, C(5)H₃, and C(6)H₃), 6.14–6.07 (m, 1H, C(7)H), 4.18 [d, 1H, J = 8.0 Hz, C(8)H₃], 2.28 [B of AB, 1H, J₆₂ = 17.3 Hz, one of C(2)H₂], 2.20 [A of AB, 1H, J₆₂ = 17.3 Hz, one of C(2)H₂], 1.31, 1.14 [2 × s, 2 × 3H, C(3)(CH₃)], 0.76 [s, 3H, C(8a)CH₃]. 13C{¹H} NMR (CDCl₃, 75.5 MHz): δ 218.5 (C), 127.1 (CH), 126.8 (CH), 125.3 (CH), 119.7 (CH), 109.6 (C), 84.9 (CH), 50.1 (CH), 40.7 (C), 38.6 (C), 28.8 (CH₃), 28.6 (CH₃), 11.4 (CH₃). Also isolated as a side product during the aromatic addition reaction of α-diazoketone 11 was the side product: 5-(Methyl-phenylhexane-2,3-dione (34) (88% yield). An aqueous solution of sodium azide (10 mL, 30 mmol, 3.0 M, 3.0 mL min⁻¹) was pumped through a micro mixer T-piece where it met a dichloromethane solution of triethyl azide (10 mL, 5 mmol, 0.5 M, 3.0 mL min⁻¹); the combined biphasic stream was passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.2 mL min⁻¹ to give a residence time of 1 h for triethyl azide generation. The reactor effluent for the first step passed through a T-piece where it met a stream of saturated aqueous sodium bicarbonate (0.1 mL min⁻¹). The combined stream was passed through a back pressure regulator (8 bar). The biphasic effluent was then separated by an in-line liquid–liquid separator and the dichloromethane effluent (25 mL), containing triethyl azide (22), was collected over KOH pellets. The separated dichloromethane triethyl azide solution (25 mL, 0.17 mL min⁻¹) was pumped to a T-piece where it met a dichloromethane solution of 2,5-dimethyl-1-phenyl-3,4,5-trimethylphenylhexane-1,3-dione (18) and DBU (25 mL, 3 mmol, 0.12 M, [DBU] 0.128 M, 0.17 mL min⁻¹), and the combined stream was then passed through a reactor coil (4 × 10 mL, rt, 120 min residence time). The diazo-transfer effluent (75 mL) was also collected over KOH pellets, and a 25 mL portion, containing the α-diazoketone 11, was pumped forward to undergo aromatic addition; this 25 mL solution was passed through a silica gel plug (glass column, 100 mm × 10 mm internal diameter, rt, 0.75 mL min⁻¹) to remove polar components. Immediately after eluting from the silica gel plug, the effluent was passed through a packed bed reactor containing IPB catalyst 9 (0.417 g, 10 mol % based on 19, glass column, 150 × 66 mm internal diameter, 0.75 mL min⁻¹, 45°C). The reactor effluent containing azulene 32 was collected in a flask containing PTAD (0.175 g, 1.0 mmol) in dichloromethane (10 mL). Once all the effluent was collected, the contents of the flask were stirred for 1 h at room temperature. The reaction solution was analyzed by IR spectroscopy and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with hexane/ethyl acetate (97:3) as eluent afforded the adduct 10 as a white solid (0.121 g, 30%, 82% ee). [α]_D²⁰ +64.38 (c 0.08, CHCl₃), ν_m (cm⁻¹) (ATR): 3042, 2926, 1747 (CO), 1715 (CO).
This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{t} \text{er}- \text{B} \text{utyl-2-cyano-2-diazo-N-} (4' \text{-} \text{chlorobenzyl}) \text{acetamide (56).}^{71}

This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{t} \text{er}- \text{B} \text{utyl-2-cyano-2-diazo-N-} (4' \text{-} \text{fluorobenzyl}) \text{acetamide (57).}^{71}

This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-N-(4'-fluorobenzyl)acetamide (50), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{fluorobenzyl}) \text{acetamide (58).}^{71}

This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-2-diazo-N-(4'-fluorobenzyl)acetamide (58), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}

This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-2-diazo-N-(4'-methylbenzyl)acetamide (51) (and triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}

This compound was prepared according to the general flow procedure from N-tert-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}

This compound was prepared according to the general flow procedure from N-tet-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}

This compound was prepared according to the general flow procedure from N-tet-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}

This compound was prepared according to the general flow procedure from N-tet-butyl-2-cyano-N-(4'-chlorobenzyl)acetamide (48), triethylamine (25 mL, 0.12 M, [NEt3] 0.128 M), aqueous sodium azide (10 mL, 3.0 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording \( \text{N-} \text{ter}- \text{t} \text{uty} \text{l-2-cyano-2-diazo-N-} (4' \text{-} \text{methylbenzyl}) \text{acetamide (59).}^{71}
azole (10 mL, 0.3 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording diazaacacetamidate 59 as a yellow crystalline solid (0.673 g, 83%). Mp: 86–88 °C (lit. 103 °C).

\[ \text{Cyclohexane ring C} \]

This compound was prepared according to the general flow procedure from N-tert-buty1-2-cyano-2-diazo-N-(4′-bromobenzyl)acetamide (52), triethylamine (25 mL, 0.12 M, [NET3] 0.128 M), aqueous sodium azide (10 mL, 0.3 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording diazaacacetamidate 60 as a yellow crystalline solid (0.818 g, 96%). Mp: 105–107 °C (lit. 110 °C).

\[ \text{Cyclohexane ring C} \]

This compound was prepared according to the general flow procedure from N-tert-buty1-2-cyano-2-diazo-N-(3′,5′-dimethylbenzyl)acetamide (53), triethylamine (25 mL, 0.12 M, [NET3] 0.128 M), aqueous sodium azide (10 mL, 0.3 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording diazaacacetamidate 61 as a yellow crystalline solid (0.587 g, 76%). Mp: 88–91 °C.

\[ H \text{ NMR (CDCl}_3, 400 \text{ MHz}): \delta 7.50 \text{ (s, 2H, C}_2\text{H}) \text{ and C}(5′\text{H})], 7.10 \text{ (s, 2H, C}_2\text{H}), 1.41 \text{ (s, 9H, C(CH}_3)_2], 1.21 \text{ (s, 6H, C(CH}_2)_2], 1.05 \text{ (s, 6H, C(CH}_2)_2], 0.83 \text{ (s, 18H, C(CH}_3)_3]. \]

\[ H \text{ NMR (CDCl}_3, 400 \text{ MHz}): \delta 14.47 \text{ (s, 3H, C}_2\text{H}), 131.9 \text{ (C), 127.7 (CH), 121.3 (C), 109.7 (C), 60.4 (C), 54.8 (C), 49.3 (CH), 28.5 (CH).} \]

N-tert-Butyl-2-cyano-2-diazo-N-(3′, 5′-dimethylbenzyl)acetamide (61).

This compound was prepared according to the general flow procedure from N-tert-buty1-2-cyano-2-diazo-N-(3′,5′-dimethylbenzyl)acetamide (53), triethylamine (25 mL, 0.12 M, [NET3] 0.128 M), aqueous sodium azide (10 mL, 0.3 M), and a dichloromethane solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M). The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (80:20) as eluent affording diazaacacetamidate 62 as a yellow crystalline solid (0.587 g, 76%).

\[ \text{Cyclohexane ring C} \]

An aqueous solution of sodium azide (10 mL, 30 mmol, 3.0 M, 3.0 mL min\(^{-1}\)) was pumped through a micromixer T-piece where it met a toluene solution of triflic anhydride (10 mL, 5 mmol, 0.5 M, 3.0 mL min\(^{-1}\)) the combined stream passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.2 mL min\(^{-1}\) to give a residence time of 1 h. The reactor effluent passed through a T-piece where it met a stream of saturated aqueous sodium bicarbonate (1:1 mL min\(^{-1}\)). The reaction stream was passed through a back pressure regulator (8 bar). The biphase reactor effluent was then separated by an in-line liquid–liquid separator. The toluene layer (25 mL) was collected over KOH pellets and was directly fed to another pump. The pump delivered the separated triflic azide solution (25 mL, 0.165 mL min\(^{-1}\)) to a T-piece where it met a DBU and toluene solution of 66 (25 mL, 3 mmol, 0.12 M, [DBU] 0.128 M) which then passed through a reactor coil (4 × 10 mL, rt, 120 min residence time), and then passed through a back pressure regulator (8 bar). The reactor effluent (100 mL) was collected over KOH pellets, from which a 25 mL portion, containing diazo-β-sulfonyl ester solution 63 was pumped forward to undergo C–H insertion; this 25 mL solution was passed through a silica gel plug (glass column, 100 mm × 10 mm internal diameter, rt, 0.5 mL min\(^{-1}\)) to remove polar components. Immediately after eluting from the silica gel plug, the effluent was passed through a packed bed reactor containing IPB catalyst 9 (0.313 g, 10 mol % based on 66, glass column, 150 × 60 mm internal diameter, 0.5 mL min\(^{-1}\), 111 °C). The reactor effluent was analyzed by IR spectroscopy and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent and afforded methyl (1R,4αR,8αS)-octahydro-1H-isothiochromene-1-carboxylate 2,2-dioxide (65) as a white solid (47 mg, 26%, 88% ee determined by chiral phase HPLC).

\[ \text{Cyclohexane ring C} \]
Hz, 3.1 Hz, C(1)H and H₆ of C(3)H₆, 2.96 (overlapping dddd, 1H, J = 14.0 Hz, 3.2 Hz, H₆ of C(3)H₆, 2.14 – 1.62 (m, 8H, C(4)H₄ C(4s) H, C(8)H) and cyclohexane ring C(6)), 1.36 – 1.14 (m, 2H, cyclohexane ring C(6)), 1.11 – 0.92 (m, 2H, cyclohexane ring C(6)).

1H NMR (CDCl₃, 75.5 MHz): δ 166.9 (C), 68.9 (CH), 52.8 (CH₂), 48.5 (CH), 43.0 (CH), 33.6 (CH), 31.1 (CH), 30.9 (CH₂), 25.5 (CH₂), 25.4 (CH₂).

**ACKNOWLEDGMENTS**

Financial support from the Irish Research Council (IRC) (D.C., GOIPG/2015/2972; T.A.B., GOIPG/2015/3188; and A.M.K., GOIPG/2018/112)), Synthesis and Solid State Pharmaceutical Centre (SSPC) supported by Science Foundation Ireland and cofunded under the European Regional Development Fund (D.L., SFI SSPC2 12/RC/2275 S and SFI SSPC3 PharmS 12/RC/2275 S), and equipment provided though a SFI research infrastructure award for process flow spectroscopy (ProSpect) (SFI 15/R1/3221) is gratefully acknowledged. Dr Brian Feerick and Paul McDowell are acknowledged for their contributions. We acknowledge the contribution of Janssen Pharmaceutical for the kind loan of one of the flow chemistry reactors used in this work.

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**Notes**

The authors declare no competing financial interest.
Excellent stereocontrol in intramolecular Buchner cyclizations and Assessment of Diazo Compounds and Diazo Transfer Reagents. Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard −

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