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Three-component reaction discovery enabled by mass spectrometry of self-assembled monolayers

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Multicomponent reactions are employed extensively in many areas of organic chemistry. Despite significant progress, the discovery of such enabling transformations remains challenging. Here, we present the development of a parallel, label-free reaction-discovery platform that can be used in the identification of new multicomponent transformations. Our approach is based on parallel mass spectrometric screening of interfacial chemical reactions on arrays of self-assembled monolayers. This strategy enabled the identification of a simple organic phosphine that can catalyse a previously unknown condensation of siloxyalkynes, aldehydes and amines to produce 3-hydroxyamides with high efficiency and diastereoselectivity. The reaction was further optimized using solution-phase methods.

The integration of innovative reaction-screening formats with analytical techniques to identify products rapidly can enable the discovery of an arsenal of new catalytic, synthetically useful processes. Despite significant progress in developing parallel reaction-screening platforms[1–19] the rapid discovery of transformations that produce products with unanticipated structures remains highly challenging. To enable the identification of such reactions, analysis of the outcome of each individual experiment must be quick, precise and structurally unbiased. Existing approaches that tackle this problem require either the conjugation of reactants to information-coding deoxyribonucleic acid strands[20–22] or the use of liquid chromatography–mass spectrometry (LCMS) or gas chromatography–mass spectrometry (GCMS) methods[23–25]. Herein we describe the development of an efficient reaction-discovery strategy that entails the screening of interfacial chemical transformations on self-assembled monolayers (SAMs) of alkanethiolates on gold using matrix-assisted laser desorption/ionization and time-of flight mass spectrometry (MALDI-TOF-MS). This general approach, which previously we termed SAMDI[26] enabled the initial identification of a new three-component reaction of amines, aldehydes and siloxyalkynes, which was optimized subsequently using solution-phase methods. This effort validated our structurally unbiased discovery strategy and uncovered a unique mode of catalytic activation of electron-rich alkynes using simple organic phosphines.

Our general screening approach starts with a glass slide that is patterned with an array of gold islands, each of which is modified with a monolayer that presents the substrate of interest. Unique combinations of reagents are applied to each of the islands to create an array of reactions, which are allowed to proceed for a specified amount of time. The reactions are stopped by rinsing the array and are then analysed rapidly by mass spectrometry to identify those combinations of reactants and reagents that give products in high yield. These 'hits' are identified easily and then can be investigated in more detail. This technique is highly sensitive (the amount of monolayer-linked substrate is on the order of picomoles per square millimetre) and because mass spectrometry is used it does not require work-up procedures to separate the products from the reaction mixture. Previously, we employed this method to a range of biochemical applications[27–30]. Furthermore, we found that the monolayers are compatible with many organic and organometallic reactions[31,32] and showed that the SAMDI method can rapidly detect all interfacial reactions that result in a mass change. This approach provides a unique opportunity for the label-free discovery of new catalytic processes.

Results and discussion

SAMDI reaction screen. Multicomponent condensations enable a rapid increase in structural complexity and molecular diversity by creating new products from more than two reactants in a single operation. Such reactions are employed extensively to generate chemical libraries[33], assemble bioactive natural products[34] and invent organocatalytic transformations[35]. Despite significant progress, the discovery of new multicomponent transformations remains challenging. As part of our ongoing investigation of the basic reactivity of siloxyalkynes, we decided to take advantage of the unique chemical profile of this class of organosilanes to develop new multicomponent reactions. Previously, siloxyalkynes were found to participate in a series of catalytic carbon–carbon and carbon–heteroatom bond-forming reactions[36–41]. Depending on the mode of activation, such electron-rich alkynes undergo reactions with either nucleophiles[36–39] or electrophiles[40,41]. Thus, we anticipated that a single catalyst could promote a three-component condensation of a siloxyalkyne with two other reaction partners of opposite electronic properties, for example a carbonyl-based electrophile and an amine-containing nucleophile. Although various reaction products are expected from such a three-component combination, we wondered whether the SAMDI method could identify efficiently the formation of new products and enable substantial variation of possible reactants, catalysts, additives and solvents en route to such discovery.

We created screening arrays by first treating glass substrates with a dilute solution of (tridecafluoro-1,1,2,2-tetrahydrooctyl)-1-trichlorosilane and then masking the substrate with a stencil to deposit titanium (10 nm) followed by gold (100 nm) in a pattern of islands. The fluorinated surface that surrounded the islands served to confine wetting by a wide range of organic solvents and therefore kept the droplets on each monolayer in place and separate from each other. This platform is compatible with most non-fluorinated solvents. Next, monolayers were prepared by treating the gold

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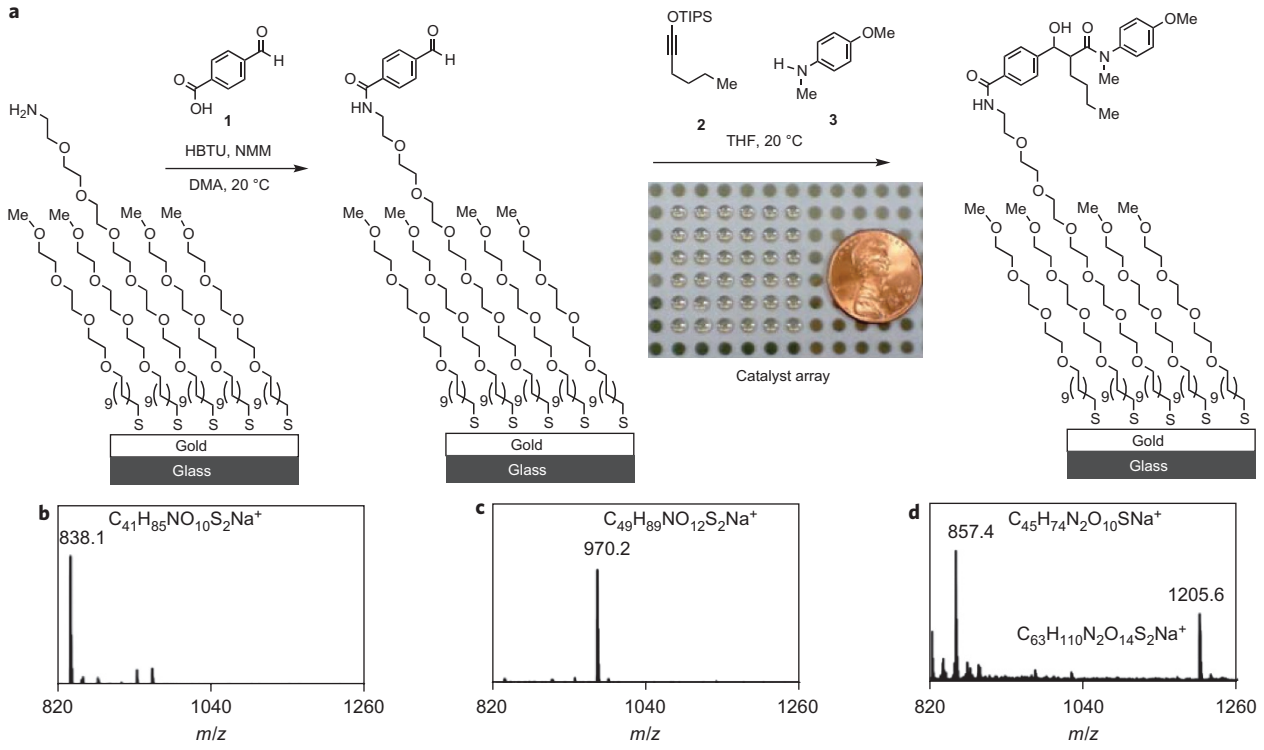


Figure 1 | Discovery of a new three-component reaction by SAMDI. a, The reaction screen was set up by first immobilizing aldehyde **1** to the monolayer, followed by exposure of the resulting monolayer to **2** and **3** in the presence of various possible catalysts. **b**, SAMDI spectrum of the amine-terminated monolayer. **c**, SAMDI spectrum of an aldehyde-functionalized monolayer synthesized via amide coupling. **d**, SAMDI spectrum of a new three-component product formed in one of the interfacial reactions.

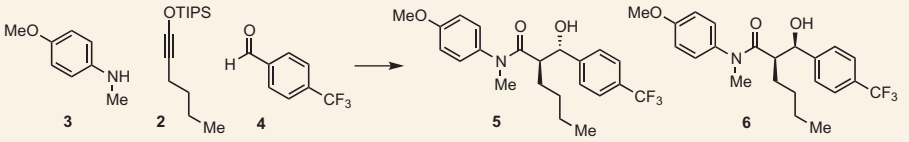
islands with an ethanolic solution of an amine-terminated alkanethiol that contained multiple ethylene glycol spacers and a similar methyl ether-terminated alkanethiol with a tris(ethylene glycol) spacer (Fig. 1a). The latter served as an inert background to control the density of reactive amine-containing functional groups on the monolayer surface. Figure 1b shows a mass spectrum of the monolayer formed initially and reveals a peak at m/z 838.1 that corresponds to the sodium adduct of a mixed disulfide derived from the amine-containing and methyl ether-terminated alkanethiolate.

We introduced the aldehyde functionality by treating the amino-terminated monolayer with 4-formylbenzoic acid (**1**), *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluranium hexafluorophosphate (HBTU) and *N*-methylmorpholine (NMM). The monolayer was rinsed, dried and analysed by SAMDI to reveal a new peak at m/z 970.2 (Fig. 1c), which corresponds to the sodium adduct of a mixed disulfide composed of a methyl ether-terminated alkanethiolate and another alkanethiolate that contains the newly installed aldehyde. This method of immobilizing substrates could be applied to introduce other functional groups of interest (for example, alkynes and alkenes) onto monolayers and avoids the need to synthesize functionalized alkanethiols prior to the assembly of the monolayer.

To perform the reactions we applied a solution of 1-siloxy-1-hexyne (**2**) and 4-methoxy-*N*-methyl aniline (**3**) in tetrahydrofuran (THF, Fig. 1a) to each aldehyde-terminated monolayer spot followed by the addition of a potential catalyst in THF with a 10:5:1 molar ratio of **2**:**3**:catalyst. We evaluated several common Lewis acids, Brønsted acids and transition-metal complexes (Supplementary Fig. S1). The screening array was assembled under a nitrogen atmosphere to prevent degradation of air- and moisture-sensitive reagents, after which it was transferred to a glass chamber saturated with THF to prevent solvent evaporation after all the reagents had been added. The reactions were allowed to proceed for 30 minutes at room temperature, and then the monolayer array was rinsed with acetone, THF and ethanol. After drying, the array was treated with 2,5-dihydroxybenzoic acid and each spot was analysed by MALDI-TOF-MS. The majority of conditions screened revealed that no reaction occurred with the immobilized aldehyde (Supplementary Fig. S1). For example, a mass spectrum of the reaction that contained only siloxyalkyne **2** and amine **3** in THF showed a single peak at m/z 970.2 (Fig. 1c), which corresponds to the starting aldehyde. Although most of the conditions screened yielded no detectable or unidentified products, the mass spectrum from a reaction spot that contained $Pd(PPh_3)_4$ revealed the formation of new peaks at m/z 857.4 and 1205.6 (Fig. 1d), consistent with the sodium adduct of an alkanethiolate terminated in a product derived from **1**, **2** and **3**, with loss of the triisopropylsilyl (TIPS) group as well as the sodium adduct of a mixed disulfide produced from this three-component product and the background methyl ether-terminated alkanethiolate. SAMDI simultaneously provided data on the presence of both the reactants and potential products, so this analytical technique can be used to assess qualitatively the conversion achieved in an interfacial reaction. In the mass spectrum from this reaction spot (Fig. 1d), no peaks derived from the unreacted aldehyde could be detected, which indicates that this reaction proceeded efficiently on the monolayer.

Solution-phase optimization. We began a detailed investigation of this novel transformation by performing the reaction in solution under the conditions initially found in the primary SAMDI reaction screen. The first evaluation of several aldehydes revealed that 4-(trifluoromethyl)benzaldehyde (**4**) displayed the highest reactivity. We found that subjecting **4** to siloxyalkyne **2** and aniline **3** in the presence of $Pd(PPh_3)_4$ (20 mol%) and MeOH

Table 1 | Effect of catalysts, additives and solvents on the solution-phase reaction.



Entry	Catalyst (mol%)	Additive (equiv.)	Solvent, temperature (°C)	Conversion (%)	d.r.
1	$Pd(PPh_3)_4$ (5)	MeOH (5)	THF, 20	56	85:15
2	$Pd(OAc)_2$ (5)	MeOH (5)	Toluene, 20	<2	
3	$Pd(PCy_3)_2$ (5)	MeOH (5)	Toluene, 20	35	85:15
4	$Pd(PPh_3)_4$ (5)	MeOH (5)	Toluene, 60	65	85:15
5	Ph_3P (20)	MeOH (5)	Toluene, 60	50	88:12
6	$(4\text{-}MeC_6H_4)_3P$ (10)	MeOH (2.5)	Toluene, 60	60	91:9
7	$(4\text{-}MeOC_6H_4)_3P$ (10)	MeOH (2.5)	Toluene, 60	75	91:9
8	$(4\text{-}MeOC_6H_4)_3P$ (20)	BnOH (2)	Toluene, 60	89	91:9
9	$(4\text{-}MeOC_6H_4)_3P$ (20)	$4\text{-}FC_6H_4CH_2OH$ (2)	Toluene, 60	96	91:9

The experiments were performed by treating a solution (0.5 ml) of **3** (0.25 mmol), **2** (0.37 mmol) and **4** (0.50 mmol) with the specified catalysts and additives listed above. After 24 hours, an aliquot of the reaction was concentrated *in vacuo*, dissolved in $CDCl_3$ (0.50 ml) and analysed by ^1H NMR spectroscopy. For each run, conversion and diastereoselectivity were calculated based on the consumption of 4-methoxy-*N*-methylaniline (**3**) and the formation of products **5** and **6**. Diastereomeric ratios (d.r.) were determined by 500 MHz ^1H NMR analysis of the crude reaction mixtures prior to chromatographic purification.

(5 equiv.) in THF at 20 °C produced an 85:15 mixture of the two diastereomeric products **5** and **6** with 56% conversion, as monitored by ^1H NMR spectroscopy (Table 1, entry 1). We determined the structure of the major *anti*-product **5** using NMR and mass spectrometry, and subsequent X-ray crystallographic analysis. Also, we found that the presence of methanol in the reaction mixture was critical to the reaction. Although a proton source was not introduced specifically during the initial reaction screening on SAMs, we believe that adventitious moisture could have served this role in the interfacial reaction.

Previously Pd complexes had not been found to promote any reactions of siloxyalkynes and the role of this metal in the three-component reaction was not evident, so we examined other Pd-containing compounds. Interestingly, although $Pd(OAc)_2$ gave none of the previously observed products (Table 1, entry 2), a Pd complex that contained another phosphine ligand produced the same outcome as $Pd(PPh_3)_4$, albeit with a lower efficiency (Table 1, entry 3). Raising the temperature of the reaction to 60 °C resulted in an increase of reaction efficiency (Table 1, entry 4). As only phosphine-containing complexes had proved effective thus far, we decided to perform the same reaction in the presence of only PPh_3 and MeOH, with the complete exclusion of Pd. Under such conditions, the same three-component product was obtained with similar efficiency and diastereoselectivity to those of $Pd(PPh_3)_4$ (Table 1, entry 5), which strongly suggests that the presence of a transition metal was not required for this reaction. PPh_3 was not included in the primary SAMDI reaction screen, so the effect of this compound (which is typically used as a transition-metal ligand) as the sole reaction promoter was not evaluated at an earlier stage.

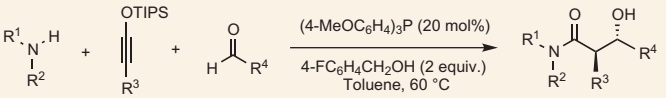
To increase the efficiency of the solution-phase three-component condensation of **2**, **3** and **4**, next we evaluated a variety of phosphines, other nucleophilic reagents and a range of proton sources. Selected results of our extensive studies are summarized in Table 1 (entries 6–9). We found that electron-rich triarylphosphines were the most reactive in promoting the desired transformation, with tris(4-methoxyphenyl)phosphine being the best catalyst with methanol as the additive (Table 1, entry 7). Throughout the optimization studies, replacing methanol with benzyl and 4-fluorobenzyl alcohols improved the diastereoselectivity of this process further (to 91:9) and also increased the reaction efficiency (Table 1, entries 8 and 9). During these studies, we established that one equivalent of the alcohol is required for the quantitative transfer of the TIPS group. With complete exclusion of a phosphine or its substitution by phosphine oxides no three-component reaction was observed, which indicates that a combination of a phosphine with an appropriate alcohol additive was responsible uniquely for a successful product formation and catalytic turnover. This finding is very significant because prior to this study simple organic phosphines were not known to catalyse any reactions of siloxyalkynes.

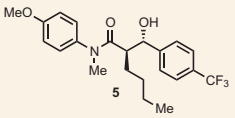
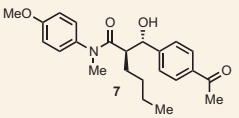
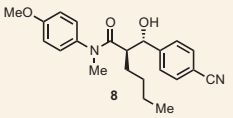
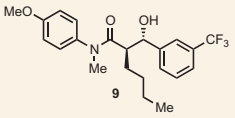
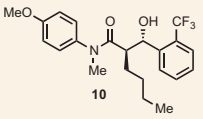
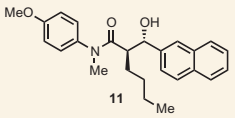
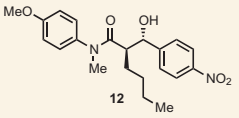
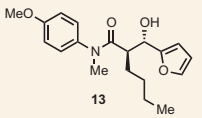
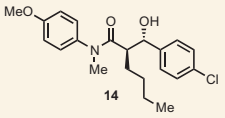
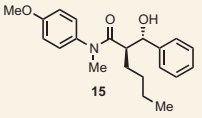
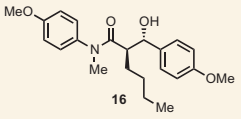
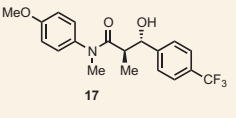
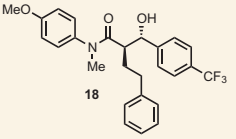
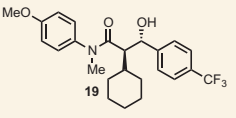
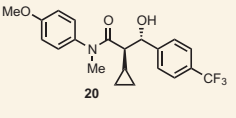
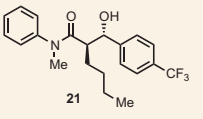
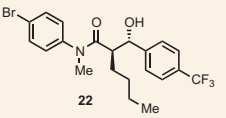
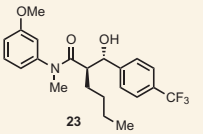
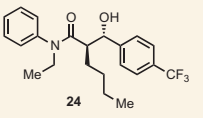
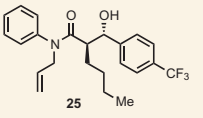
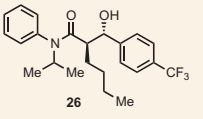
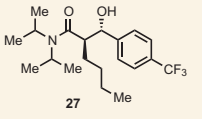
Reaction scope study. Next, we examined a series of aromatic aldehydes that could participate in a phosphine-catalysed three-component condensation with alkyne **2** and amine **3**. The major product **5** of the parent reaction with 4-(trifluoromethyl)-benzaldehyde (**4**) was isolated in 87% yield (Table 2, entry 1), fully consistent with the high degree of conversion observed in previous NMR spectroscopic studies. Under the same reaction conditions, other electron-deficient benzaldehydes afforded the expected products with good yields and high diastereoselectivity (Table 2, entries 2–7). Both *ortho*- and *meta*-aromatic substitutions of the aldehyde were well tolerated. Interestingly, the reaction of a ketone-containing aldehyde (Table 2, entry 2) proceeded with complete chemoselectivity, with only the aldehyde being reactive under the conditions of the three-component reaction. Also, heteroaromatic and halogen-containing aldehydes reacted efficiently (Table 2, entries 8 and 9), but unsaturated and aliphatic aldehydes gave lower yields, presumably because of other reactions promoted by secondary amines, including enolization of aliphatic aldehydes and conjugate additions to unsaturated aldehydes.

Also, we examined the scope of the reaction with regard to siloxyalkyne substitution. The use of 1-siloxy-1-propyne resulted in the desired product in high yield with slightly diminished diastereoselectivity (Table 2, entry 12). The presence of aromatic groups in the siloxyalkyne structure was tolerated well (Table 2, entry 13). Furthermore, introduction of bulky substituents, such as cyclohexyl or cyclopropyl groups, in direct proximity to the alkyne moiety did not seem to impact the efficiency or the diaseteroselectivity of the reaction (Table 2, entries 14 and 15). Such results suggest that a wide range of siloxyalkyne substitution would be well tolerated in the three-component reaction.

The final aspect of the scope study entailed the evaluation of a series of amines. Secondary anilines proved to be the most suitable substrates for this reaction. This observation is not surprising because most of the initial optimization work was performed employing aromatic amines, which displayed the most promising reactivity profile. For instance, *N*-methylaniline, *N*-methyl-4-bromoaniline and *N*-methyl-3-methoxyaniline produced the corresponding three-component reaction products **21**–**23** in 61–74%

Table 2 | Scope of the three-component condensation of aldehydes, siloxyalkynes and amines.



Entry	Major product	Yield (%)	d.r.
1	 **5**	87	91:9
2	 **7**	87	88:12
3	 **8**	73	88:12
4	 **9**	63	91:9
5	 **10**	74	93:7
6	 **11**	68	91:9
7	 **12**	66	84:16
8	 **13**	59	88:12
9	 **14**	63	90:10
10	 **15**	58	91:9
11	 **16**	44	84:16
12	 **17**	75	85:15
13	 **18**	72	91:9
14	 **19**	80	91:9
15	 **20**	87	91:9
16	 **21**	76	91:9
17	 **22**	74	95:5
18	 **23**	61	91:9
19	 **24**	78	88:12
20	 **25**	57	89:11
21	 **26**	52	80:20
22	 **27**	30	63:37

All reactions were carried out according to the general procedure described in the Methods section. The yields refer to those isolated for the major diastereomeric product of each three-component reaction after chromatographic purification. Diastereomeric ratios were determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures prior to chromatographic purification.

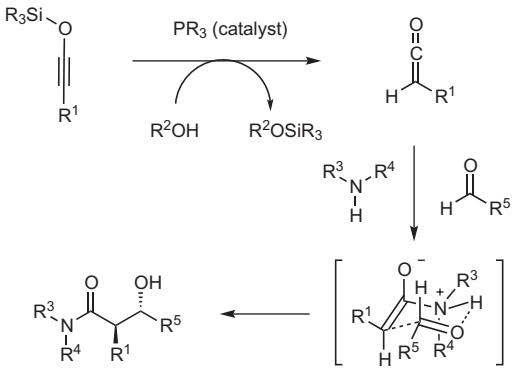


Figure 2 | Proposed mechanism of the phosphine-catalysed three-component reaction of siloxyalkynes with amines and aldehydes. The mechanism involves the initial desilylation of the siloxyalkyne, which is promoted by phosphine and alcohol, followed by reaction of the resulting ketene with amine and aldehyde to generate the observed three-component product. The stereochemistry of the final product can be rationalized based on the chair-like transition state shown.

isolated yields (Table 2, entries 16–18). Other *N*-substituted anilines participated readily in this reaction (Table 2, entries 19–21). Not surprisingly, increasing the steric bulk of the *N*-alkyl substituent resulted in lower yields of the desired product, as well as a diminished diastereoselectivity. Although primary anilines did not afford any three-component products under the same reaction conditions, *N,N*-dialkylamines displayed a variable pattern of reactivity and diastereoselectivity. For instance, the three-component reaction using diisopropylamine afforded the desired major *anti*-diastereomeric product in a decreased isolated yield as a result of a diminished level of diastereoselection (Table 2, entry 22).

With the reaction scope established, next we demonstrated the utility of this three-component transformation for the rapid synthesis of a representative small-molecule library of hydroxyamides, which was generated from three siloxyalkynes, three aldehydes and four amines (Supplementary Fig. S2). The library was produced and purified by mass-triggered preparative LCMS to deliver successfully 36 requisite compounds on a 20–66 mg scale in high chemical purity (see Supplementary Information).

Formation of the observed three-component products can be rationalized tentatively based on the mechanism depicted in Fig. 2. Reaction of a siloxyalkyne with phosphine and alcohol is expected to produce a ketene. This step is supported by our deuterium-incorporation studies using a deuterated alcohol (R^2–OD), which demonstrated exclusive incorporation of deuterium at the α-position of the carbonyl group in the final three-component product. During the course of the reaction the silyl group is transferred solely to the corresponding silyl ether (R^2–$OSiR_3$), as shown in Fig. 2. Subsequent addition of the secondary amine to a ketene, followed by an aldol reaction with an aldehyde, would generate the observed hydroxyamide product. The closed transition state shown in Fig. 2 could explain the predominant formation of the major *anti*-diastereomer. The proposed mechanism is supported further by a range of other experiments, including the preliminary kinetic analysis of this process.

Other phosphine-catalysed reactions of siloxyalkynes. We also identified several other phosphine-catalysed transformations of siloxyalkynes that are fully consistent with the possible generation of ketenes under the reaction conditions. For example, treatment of siloxyalkyne **28** with amine **30** in the presence of tris(4-methoxyphenyl)phosphine (20 mol%) and 4-fluorobenzylalcohol (2 equiv.) at 20 °C afforded the corresponding amide **31** in 95% yield (Fig. 3a). The primary aniline **32** was also employed under

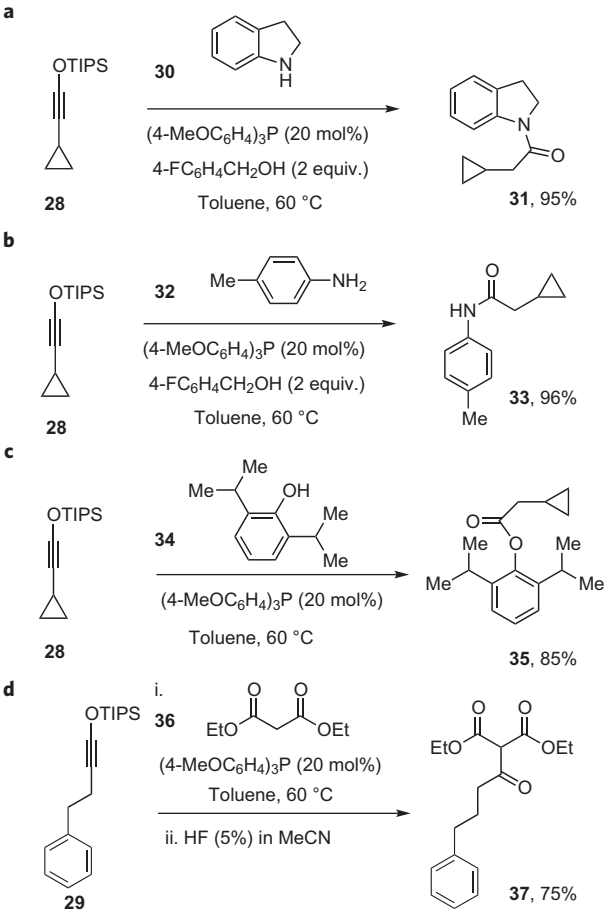


Figure 3 | Other representative phosphine-catalysed reactions of siloxyalkynes. a–d, Such reactions include amidations of siloxyalkynes with aliphatic (**a**) and aromatic (**b**) amines, esterification of a siloxyalkyne with highly hindered phenols (**c**) and condensation of a siloxyalkyne with diethyl malonate (**d**).

the same conditions to afford amide **33** (Fig. 3b). Furthermore, treatment of siloxyalkyne **28** with the hindered phenol **34** yielded the corresponding ester **35** in high yield (Fig. 3c). Two equivalents of the alcohol were required in this experiment, as one equivalent was converted into the corresponding TIPS ether. Finally, we examined whether phosphine catalysis enabled *C*-acylation of malonates with siloxyalkynes. Treatment of malonate **36** with alkyne **29** in the presence of tris(4-methoxyphenyl)phosphine (20 mol%) followed by desilylation with HF afforded the *C*-acylated product **37** (Fig. 3d). The above phosphine-catalysed reactions of siloxyalkynes with several classes of commonly used nucleophiles offer unique and exceedingly mild reaction conditions for such transformations and further expand the newly identified concept of nucleophilic activation of this class of organosilicon compounds.

Conclusions

The work described herein establishes that SAMDI-based screening can be used to identify novel multicomponent reactions. This method does not require labels to identify specific products, is well suited to the discovery of transformations that give products with structures not predicted easily from prior knowledge of substrate reactivity and is adaptable to multiparameter reaction screening. This effective reaction-screening strategy enabled the discovery of the first three-component reaction of siloxyalkynes with aldehydes and amines and uncovered a conceptually novel mode of

catalytic activation of electron-rich alkynes using simple organic phosphines.

Methods

Preparation of monolayers and SAMDI reaction screen. Glass slides (50 × 35 mm) were placed in a dilute solution of (tridecafluoro-1,1,2,2-tetrahydrooctyl)-1-trichlorosilane (1 vol% in anhydrous toluene) for ten minutes to create a fluorinated glass surface. The resulting slides were rinsed with acetone, sonicated in ethanol twice for 20 minutes and heated to 80 °C for two hours. The glass platform was masked with a stencil (made from aluminium) that contained evenly spaced holes with a diameter of 2.5 mm and centre-to-centre distance of 4 mm. Titanium (10 nm) and then gold (100 nm) were evaporated onto the masked glass substrate using an electron-beam evaporator (Thermionics VE-100) at a rate of 0.2 Å s^{-1} for titanium and 0.4 Å s^{-1} for gold, and at a pressure of less than 5×10^{-7} Torr, to generate the array of gold-coated islands. Then, the modified glass plate was immersed for 12 hours in an ethanolic solution (1.5 ml) that contained the background methyl ether-terminated alkanethiol and aminofunctionalized alkanethiol (for structures, see Fig. 1b) in a 3:2 ratio (total concentration 0.2 mmol l^{-1}). Next, the monolayer was treated with 2,5-dihydroxybenzoic acid (1 μl of a 10 mg m l^{-1} solution in acetonitrile), allowed to air dry and analysed on a 4800 MALDI-TOF/TOF Biospectrometry mass spectrometer (Applied Biosystems, Framingham, MA) equipped with a 355 nm neodymium-doped yttrium aluminium garnet laser and using a positive-ion reflector mode. Aldehyde **1** was immobilized by immersing the amine-functionalized monolayer in a solution that contained 4-formylbenzoic acid (100 mmol l^{-1}), HBTU (100 mmol l^{-1}) and NMM (200 mmol l^{-1}) in *N*,*N*,-dimethylacetamide (DMA). The reaction was allowed to proceed for 30 minutes at 20 °C. This process was repeated and the slides were rinsed with acetone, dried under a stream of nitrogen and analysed by MALDI-TOF-MS, as described above. Then the array was placed in a glove bag filled with nitrogen and each reaction spot was treated with 3 μl of a solution of alkyne **2** (0.67 mol l^{-1}) and amine **3** (0.33 mol l^{-1}). After addition of all the reagents, 1 μl of a solution of a potential catalyst (0.2 mol l^{-1}) in THF was applied to each spot. The array was transferred to a glass chamber saturated with THF and the reactions were allowed to proceed for 30 minutes at 20 °C. Next, monolayers were rinsed with acetone, THF and ethanol, and dried under a stream of nitrogen. Each reaction spot was treated with 2,5-dihydroxybenzoic acid (1 μl per spot of a 10 mg l^{-1} solution in acetonitrile) and analysed by mass spectrometry, as described above.

General procedure for the three-component condensation of siloxyalkynes, aldehydes and amines. All solution-phase reactions were performed under an atmosphere of argon in flame-dried (10 × 75 mm) test tubes equipped with stir bars and sealed with rubber septa. A solution of tris(4-methoxyphenyl)phosphine (35.2 mg, 0.1 mmol, 20 mol%), amine (0.5 mmol) and siloxyalkyne (0.75 mmol) in toluene (1.0 ml) was treated with aldehyde (1.00 mmol) and 4-fluorobenzyl alcohol (0.109 ml, 2.00 mmol). The resulting solution was heated to 60 °C for 48 hours. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (1.0 ml), concentrated by rotary evaporation and subjected to purification by flash chromatography to afford the resulting three-component products shown in Table 2.

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Author contributions

T.J.M. and J.L. contributed equally to the work. J.L. performed and analysed all interfacial reactions on monolayers. T.J.M. carried out most of the solution-based studies. J.R.C-P. assisted with scope studies. M.M. and S.A.K. equally provided project management. The manuscript was written by T.J.M., J.L., S.A.K. and M.M.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.M. and S.A.K.