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Diastereoselective intramolecular SmI_2–H_2O–amine mediated couplings †

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The SmI_2–H_2O–amine mixture has been shown to be effective for intramolecular couplings providing diastereoselectivities of up to 100% de in the coupling of *O*-cyclohexenyliodophenol derivatives into heterocycles.

There has been an extraordinary development of SmI_2 mediated reactions for some 20 years, ever since Kagan's breakthrough in the late 70's.[1] SmI_2 in THF has proven useful not only in the reductions of functional groups,[2] pinacol-coupling reactions[3] and as a coupling reagent between alkyl halides and ketones or olefins,[4] but also in sequential reactions.[5] Recently we discovered that a mixture of SmI_2 in THF, water and an amine (*e.g.* Et_3N, TMEDA or PMDTA) resulted in unexpected rates in the reduction of ketones, imines, α,β-unsaturated esters and alkyl halides.[6] We also found that these powerful mixtures of SmI_2–H_2O–amine reduced conjugated double bonds selectively and rapidly in the presence of isolated double bonds at room temperature.[7] It was therefore natural to investigate also the possibility of intra- and intermolecular couplings to generate carbon–carbon bonds using this protocol. A wide variety of alternative synthetic methods for this type of coupling are also available, *e.g.* H_3PO_2–AIBN,[8] Bu_3SnH–AIBN,[9] Heck coupling,[10] Michael addition,[11] photocyclisation[12] and electrochemical cyclisation.[13]

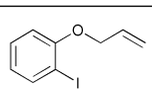
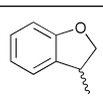
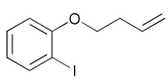
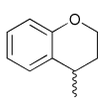
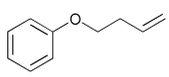
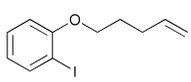
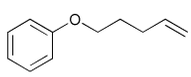
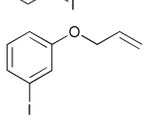
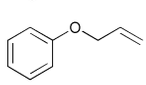
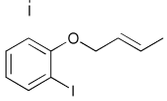
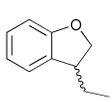
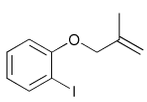
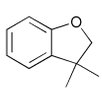
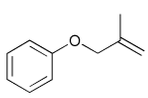
Herein we would like to present our recent developments of intramolecular SmI_2–H_2O–amine mediated couplings between aryl iodides and olefins into heterocycles in THF.

First 1-allyloxy-2-iodobenzene (**1**) was synthesised to establish whether this type of coupling was achievable at all. Mixing of SmI_2, Et_3N, **1** followed by H_2O gave an almost instantaneous reaction and the product was isolated and characterised by ^{1}H-NMR, COSY and GC/MS. We found that the reaction yielded only one product, the coupled product 3-methyl-2,3-dihydrobenzofuran (**1a**). Analogue substrates containing longer alkyl chains were also investigated for intramolecular coupling using SmI_2–H_2O–amine. The formation of five-membered rings was largely favoured over six- and seven-membered rings in these substrates (Table 1, entry 2 and 3) and increasing amounts of reduction occurred as the chain grew longer. Note that the isolated double bond was not affected even in excess SmI_2–H_2O–amine mixtures (entry 3). Interestingly the coupling was not affected by an additional methyl group at the terminal position (entry 5), while the isobutenyl isomer (entry 6) gave a coupling/reduction ratio of 80 : 20, probably due to the increased steric hindrance.

We established that in order to maximize the amount of coupled product the water had to be added gradually after the substrate to suppress the amount of reduced product. This was

† Electronic supplementary information (ESI) available: general syntheses and experimental data. See http://www.rsc.org/suppdata/ob/b3/b305428d/

Table 1 Intramolecular couplings in 1-allyloxy-2-iodobenzene analogues using SmI_2–H_2O–Et_3N[a]

Entry	Substrate		Product(s) Coupled (a)	Reduced (b)	Yield(s)[b]
1		(**1**)			>99
2		(**2**)			60 : 40[c]
3		(**3**)			> 99
4		(**4**)			> 99
5		(**5**)			> 99
6		(**6**)			80/20[d]

[a] In a standard procedure SmI_2 (2.5–3 equiv.), Et_3N (7.5 equiv.), substrate (0.1–0.2 mmol, 1 equiv.) and H_2O (12.5 equiv.) were mixed at 20 °C. H_2O was added last during 1–5 minutes under vigorous stirring. [b] Corresponding to the yields and ratios observed on GC. No substrate was observed. Close to quantitative yields were obtained on larger scale. [c] The coupling : reduction ratio was improved to 72 : 28 when *n*-butylamine was used instead of Et_3N. [d] The coupling : reduction ratio was improved to 87 : 13 when *n*-butylamine was used instead of Et_3N.

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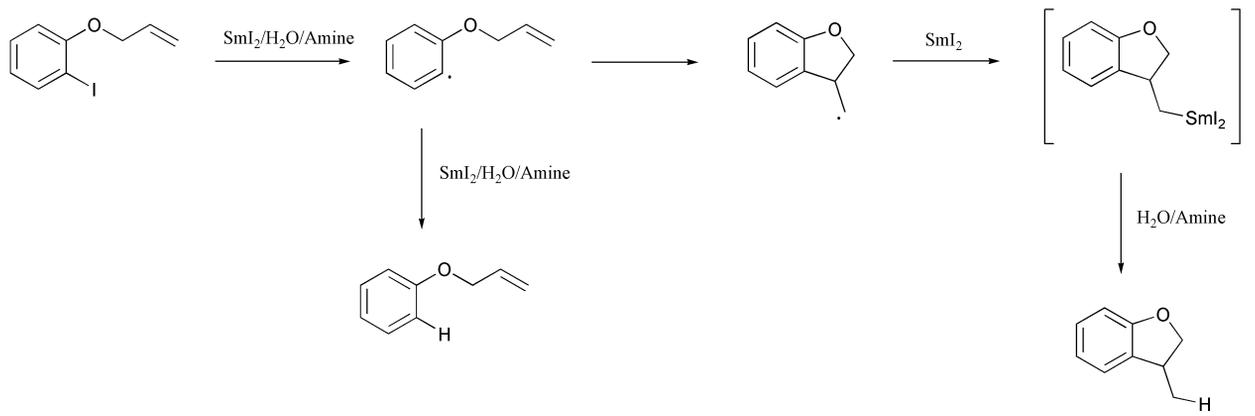


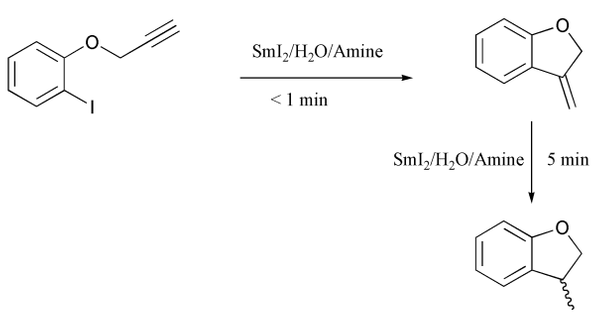
Scheme 1 Suggested mechanisms for the SmI_2 mediated coupling and reduction.

particularly significant for substrates that coupled into six-membered rings. Adding the substrate last, *i.e.* with SmI_2, Et_3N and H_2O premixed, caused the product ratio in entry 2 (Table 1) to change from 60 : 40 to 30 : 70 in favour of the reduced product. Replacing the iodide with bromide in the substrates in Table 1 resulted in longer reaction times and substantially lower amounts of coupling, *i.e.* the reduced product was favoured.

Curran and co-workers have investigated the mechanism of the samarium Barbier reaction (or samarium Grignard reaction),[14] and they concluded that the coupling reaction is most likely to occur *via* an organosamarium intermediate. A suggested mechanism in Scheme 1 includes both the coupling and the reduction reactions. Based on this it is obvious why the order of and slow addition of water is crucial for the success of this reaction.

To obtain fast and complete coupling/reduction of these substrates the proportion between SmI_2, H_2O and amine have to be at least 1 : 3 : 3, which is required for full precipitation of the samarium- and iodide salts, according to titrations.[6]

We were also interested in the intramolecular coupling of triple bonds with phenyl iodide. The coupling of 1-iodo-2-(2-propynyloxy)benzene (**7**) provided initially the corresponding five-membered styrene derivative ring (Scheme 2), which within five minutes was reduced to 3-methyl-2,3-dihydrobenzofuran (**7a**) in excess SmI_2–H_2O–amine. Similar behaviour was observed for the analogue substrate **8**, although in addition larger amounts of uncoupled reduced products were formed.



Scheme 2 Coupling of 1-iodo-2-(2-propynyloxy)benzene (**7**) followed by reduction of the conjugated double bond.

In order to examine the influence of electronic properties in these couplings a few nitrogen containing analogues to the substrates in Table 1 were also synthesised (Table 2, entry 3–5).

Interestingly the formation of the six-membered ring was improved to 70 : 30 (coupling–reduction) for the pyridine analogue (entry 4). However, a 9 : 91 ring *vs.* reduction ratio was obtained when the same substrate was added subsequent to SmI_2, Et_3N and water. In entry 5 a ratio close to 50 : 50 was obtained regardless of the addition order of water and substrate, respectively.

Hexahydrodibenzofuran derivatives include the substructure of morphine and are interesting in a pharmacological point of view, since they are known to have narcotic and analgesic properties.[15] A number of racemic 1-(cyclohex-2-enyloxy)-2-iodobenzene analogues (**12**–**16**), suitable for diastereoselective coupling into hexahydrodibenzofuran derivatives (**12a**–**16a**), were synthesised to explore further the extent of this coupling (Table 3). Interestingly the only detected product was the racemic *cis*-1,2,3,4,4a,9b-hexahydrodibenzofuran, **12a**, after the coupling of **12** with SmI_2–H_2O–Et_3N.‡ Similarly only the *cis*-products of **13a**–**16a** were formed according to NOESY analysis (Fig. 1) and separation of the products on chiral stationary phase GC.

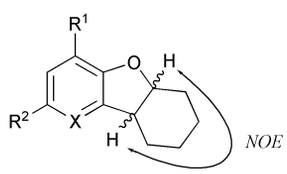
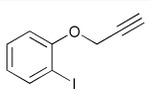
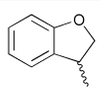
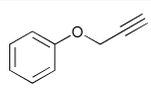
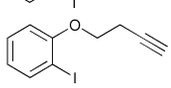
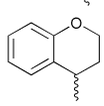
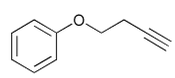
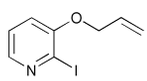
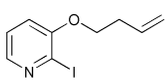
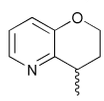
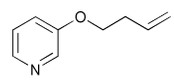
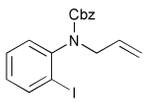
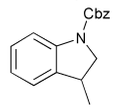
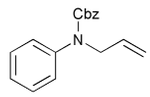


Fig. 1 NOE between the two protons on the stereogenic carbons confirming *cis*-configuration.

We noticed that different amines produced diverse coupling–reduction ratios (Table 3). Primary amines (*n*-butylamine or isopropylamine) usually increased the amount of coupled product compared to tertiary amines (triethylamine, TMEDA or PMDTA), however, the diastereoselectivity decreased slightly. Encouraged by these results we also investigated ammonia in water (~25%) as the "amine"–water source. Once again 100% de was obtained but compared to primary amines the yield was slightly lowered and in addition the reaction required approximately two hours for completion.

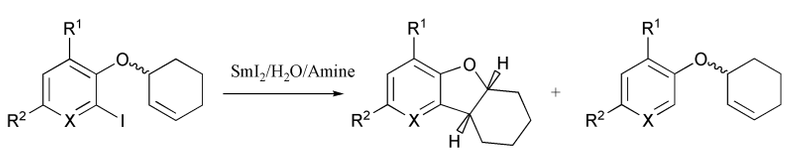
Substrates **14** and **15** were synthesised from 5-iodovanillin, additionally a third substrate (**16**) was synthesised which was protected as a 1,3-dithiane (dithioketal). Treating **16** similarly to the previously mentioned substrates we found that competing reactions occurred (Scheme 3). When **16** was treated with SmI_2(2.5 equiv.)–H_2O(7.5 equiv.)–Et_3N(7.5 equiv.), followed by quenching within 30 seconds, we could isolate the coupled product still containing the dithioketal (**16a**). However, excess SmI_2–H_2O–Et_3N gave a second product within approximately five minutes in which the dithioketal group had been opened (**16a′**). This second product was also observed in the SmI_2–NH_4OH mediated reaction after two hours of reaction time. A third product, **16a″**, was obtained after treating **16** with SmI_2–H_2O–*n*-butylamine for 1–2 hours (or several hours with Et_3N). This product was isolated in 85% yield. ^{1}H-NMR and MS showed that the 1,3-dithiane had been completely removed leaving a corresponding methyl group at this position. The complete cleavage of the dithioketal shows large resemblance to the well-known Raney Ni desulfurization protocol for

Table 2 Intramolecular couplings using SmI_2–H_2O–Et_3N [a]

Entry	Substrate		Product(s) coupled (a)	Reduced (b)	Yield(s) [b]
1 [b]		(**7**)			90 : 10 [c]
2 [b]		(**8**)			38 : 62 [c]
3		(**9**)			>99
4		(**10**)			70 : 30
5		(**11**)			50 : 50

[a] In a standard procedure SmI_2 (2.5 equiv.), Et_3N (7.5 equiv.), substrate (0.1–0.2 mmol, 1 equiv.) and H_2O (12.5 equiv.) were mixed at 20 °C. H_2O was added last during 1–5 minutes under vigorous stirring. [b] Corresponds to the yields and ratios observed on GC. No substrate was observed. [c] For entries 1 and 2 twice the amount of SmI_2, amine and water were used for complete formation of the corresponding saturated coupled products. In entry 2 the triple bond was reduced into the double bond after being left standing over night in excess SmI_2.

Table 3 Diastereoselective coupling of 1-(cyclohex-2-enyloxy)-2-iodobenzene analogues with SmI_2–H_2O–amine [a, b]



	R^1	R^2	X	12a-16a	12b-16b
12	Me	H	CH		
13	H	H	N		
14	OMe	CH_2OH	CH		
15	OMe	NH*i*Pr	CH		
16	OMe	$CH(\text{-}SCH_2\text{-})_2$	CH		

Entry	Substrate	Triethylamine a : b (% de)	*n*-Butylamine a : b (% de)	NH_4OH [c] a : b (% de)
1	**12**	72 : 28 (100)	84 : 16 (97)	75 : 25 (100)
2	**13**	92 : 8 (96)	95 : 5 (92)	40 : 60 (100)
3	**14**	85 : 15 (100)	80 : 20 (98)	60 : 40 (100)
4	**15**	77 : 23 (99.7)	85 : 15 (96)	74 : 26 (100)

[a] In a standard procedure SmI_2 (2.5 equiv.), amine (7.5 equiv.), substrate (0.2 mmol, 1 equiv.) and H_2O (12.5 equiv.) were mixed at 20 °C. H_2O was added last during 1–5 minutes under vigorous stirring. [b] Corresponding to the yields and ratios observed on GC. [c] The reactions with ammonia in water required up to 2 h reaction time for completion.

reduction of a C–S group to a C–H group. This one-pot reaction sequence may therefore also prove useful in other desulfurizations.

We also investigated the possibility of intermolecular couplings between alkyl halides and alkenes. Unfortunately all attempts were unsuccessful, and the only species found in the reaction mixtures, except for the amines, were the corresponding reduced products of the substrates.

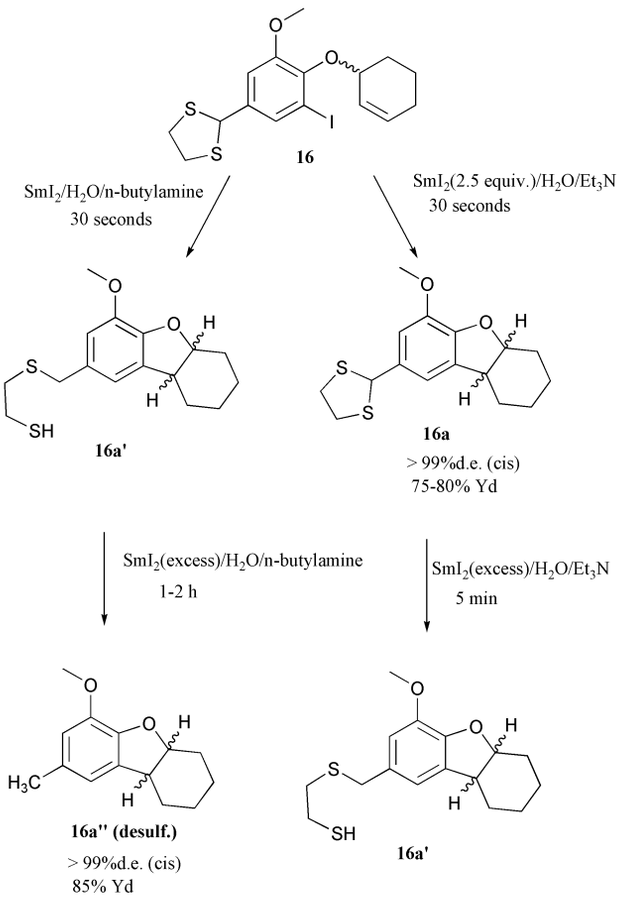
The results reported in Tables 1–3 are all performed on 0.1–0.2 mmol scale. To prove that these coupling reactions are amenable to scale up we also employed substrate **1** in larger scale (2 mmol) without any loss in chemical yield (97% isolated yield of **1a**). †

In summary, we have shown that intramolecular coupling of aryl iodides and alkenes proceeds fast under mild conditions with the recently developed SmI_2–H_2O–amine protocol. The amount of coupled product improved significantly when SmI_2, the substrate and amine were premixed followed by a gradual addition of water. Furthermore the formation of five-membered rings was preferred over six-membered rings, while formation of seven-membered rings and intermolecular coupling were unsuccessful, *i.e.* led exclusively to reduction. The coupling of 1-(cyclohex-2-enyloxy)-2-iodobenzene derivatives (**12**–**16**) yielded high or total diastereoselectivity of the formed hexahydrodibenzofuran derivatives (**12a-16a**) in good to high yields. In addition we also discovered a one-pot reaction sequence for the dithioketal protected 1-(cyclohex-2-enyloxy)-2-iodobenzene analogue (**16**), where the coupling was followed by complete removal of the dithioketal within two hours using excess SmI_2–H_2O–*n*-butylamine. The use of SmI_2–H_2O–amine in C–S bond cleavage is currently under investigation in our laboratory.

Experimental

General synthesis of substrates 1–7, 9–10 and 12–13

2-Iodophenol (3.3 g, 15 mmol) was added to a suspension of



Scheme 3 Reactions of **16** after treatment with SmI_2–H_2O–amine.

K_2CO_3 (6.2 g, 45 mmol) in DMF (50 ml) stirred under a nitrogen atmosphere. Allyl bromide (1.6 ml, 18 mmol) was added slowly by syringe and the mixture was stirred overnight. Water (50 ml) was added and the solution was extracted with *n*-hexane (4 × 50 ml). The combined organic layer was washed with water (3 × 50 ml), 10% KOH (2 × 50 ml), $Na_2S_2O_3$ (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and concentrated. Distillation under vacuum gave **1** as colourless oil (90–100% yield).

1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 2H), 5.30 (d, 1H), 5.50 (d, 2H), 6.06 (m, 1H), 6.68 (t, 1H), 6.79 (d, 1H), 7.24 (t, 1H), 7.76 (d, 1H). MS (EI) *m*/*z* 260 (M^+), 130, 102.

SmI_2–H_2O–amine mediated reaction

In a standard procedure, 5 ml SmI_2 in THF (0.5 mmol, 2.5 equiv.) was added to a dry Schlenk tube, containing a magnetic stirrer bar and fitted with a septum, inside a glove box under nitrogen atmosphere. The amine (1.5 mmol, 7.5 equiv. Et_3N) and the substrate **1** (0.2 mmol, 1 equiv.) were added under stirring. To this mixture the proton donor, *i.e.* H_2O (6.25 equiv.), was added slowly at 20.0 °C. The reaction was finished in less than one minute. To 0.2 ml of the quenched solution was added diethyl ether (1 ml) and HCl (0.1 ml, 0.12 M), or KOH (10%) for products containing nitrogen, to remove the inorganic salts and finally saturated $Na_2S_2O_3$ (5 dr) to remove excess iodine. The clear organic layer was transferred to a vial and analysed on GC and GC/MS. Evaporated samples were also analysed on ^{1}H NMR, and COSY or NOESY when considered necessary.

1a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 3H), 3.55 (m, 1H), 4.08 (t, 1H), 4.70 (t, 1H), 6.80 (d, 1H), 6.88 (t, 1H), 7.13 (t, 1H), 7.17 (d, 1H). MS (EI) *m*/*z* 134 (M^+), 119, 105, 91, 77.

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Notes and references

‡ The *cis–trans* diastereomers of the product, 1,2,3,4,4a,9b-hexahydrodibenzofuran, were synthesised as reference in two steps from dibenzofuran according to literature procedure,[16] and the chiral stationary phase GC confirmed that the two diastereomers (*cis–trans*) were well separated. The configuration of the products of the SmI_2–H_2O–amine couplings was determined by NOESY experiments.

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