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Synthesis of epoxides from aldehydes and tosylhydrazone salts catalysed by triphenylarsine: complete *trans* selectivity for all combinations of coupling partners†

Varinder K. Aggarwal,* Mamta Patel and John Studley
School of Chemistry, Bristol University, Cantock's Close, Bristol, UK BS8 1TS.
E-mail: V.aggarwal@bristol.ac.uk; Fax: (+44) 117-929861; Tel: (+44) 117-99546315

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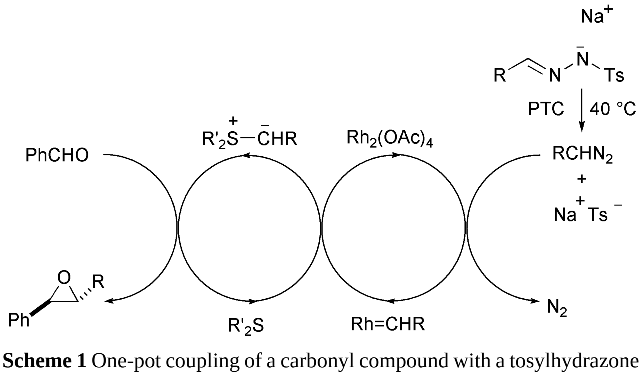
Triphenylarsine catalyses the formation of epoxides from carbonyl compounds and tosylhydrazone salts. This convergent synthesis gives complete *trans* selectivity for all aldehyde and tosylhydrazone salt coupling partners.

We recently reported a novel catalytic process for the direct coupling of aldehydes with tosylhydrazone salts to give epoxides.[1] Catalytic amounts of $Rh_2(OAc)_4$ and sulfide are employed in this process and the reaction proceeds through the intermediacy of diazocompounds, metal carbenes and sulfur ylides (Scheme 1).

Although high *trans* diastereoselectivity was observed in reactions of neutral or electron deficient aryl tosylhydrazone salts with aromatic aldehydes, much lower diastereoselectivity was observed with aliphatic aldehydes *e.g.* $C_6H_{11}CHO$ gave a 65:35 ratio of *trans*:*cis* epoxides. The problem of low diastereocontrol was further exacerbated when electron rich aryl tosylhydrazone salts were employed *e.g.* *p*-methoxyaryl tosylhydrazone salt gave a 67:33 ratio of *trans*:*cis* epoxides with benzaldehyde. The variable diastereoselectivity in the above cases results from the degree of reversibility in betaine formation. High *trans* selectivity is a consequence of reversible formation of the *syn* betaine which only cyclises slowly to give *cis* epoxide and essentially irreversible formation of the *anti* betaine which cyclises rapidly to give the *trans* epoxide. This has been proved experimentally[2] and underpinned through calculation.[3] In contrast, reaction of the same benzyl stabilised ylide with aliphatic aldehydes gives *syn* and *anti* betaines irreversibly leading to low diastereocontrol. The use of electron rich aryl-stabilised ylides leads to even less reversibility in betaine formation as the ylide is less stable and therefore again leads to low diastereocontrol. Attempts to solve this problem by changing reaction conditions were not successful so we considered more fundamental changes, and in particular the use of arsines in our catalytic process in place of sulfides.



Scheme 1 One-pot coupling of a carbonyl compound with a tosylhydrazone salt to give an epoxide, Ts = toluene-4-sulfonyl.

It is known that non-[4] or semi-stabilised[5] arsonium ylides react with aldehydes to give *trans* epoxides with high diastereoselectivity (in contrast, semi-stabilised[6] and stable[7,8] arsonium ylides react with aldehydes to give alkenes).[9] Thus, if arsines could be employed in our catalytic process not only should high *trans* selectivity result, but the potential to use sub-stoichiometric amounts and not have to manipulate the toxic reagent over several steps (as is required using conventional arsonium ylide chemistry) provides very significant operational advantages. However, literature precedent was not in our favour: although there were several reports on the formation of stable arsonium ylides through reaction of stable diazocompounds with arsines these all employed copper catalysts,[8,9a,10] which we knew were not compatible with our catalytic process. There were no examples on the use of $Rh_2(OAc)_4$ to promote ylide formation and furthermore no examples employing less stable diazo compounds which are the substrates required for epoxidation (stable diazocompounds would lead to stabilised arsonium ylides which would give alkenes).

Thus, $AsPh_3$ was initially tested in our process using benzaldehyde tosylhydrazone salt with aromatic and aliphatic aldehydes (Table 1).

We were delighted to find that the reaction was highly efficient providing high yields and complete *trans* selectivity with all of the aldehydes employed (Table 1, entries 1–5).[11] We did note that reactions with aliphatic aldehydes were slightly lower yielding and small amounts of alkene by-products were also observed (entries 3–5). Using sub-stoichiometric amounts of $AsPh_3$ high yields were again obtained with aromatic aldehydes (entries 6,7) but now a significant reduction in yield was observed with aliphatic aldehydes (entries 8–10). This was presumably due to the small amount of competing alkene formation which consumes the arsine catalyst, lowering its concentration further and preventing it from re-entering the ylide cycle. Reactions with more electron rich aryl tosylhydrazone salts were also tested. When these were employed in our sulfur ylide-mediated process low diastereoselectivity was observed even with aromatic aldehydes.[1] However, using Ph_3As complete diastereoselectivity was obtained with both aromatic and aliphatic aldehydes (entries 11–18). No competing alkene formation was observed in these cases, presumably because the intermediates are even less stabilised arsonium ylides and so epoxide formation occurs exclusively. However, whilst good yields were maintained when aromatic aldehydes were employed with sub-stoichiometric amounts of Ph_3As, a significant reduction in yield was observed with aliphatic aldehydes. We cannot account for this finding at present.

In summary, we have found that complete *trans* selectivity can be achieved in coupling reactions of aryl tosylhydrazone salts (especially those derived from electron rich aromatics) with both aromatic and aliphatic aldehydes using catalytic quantities of Ph_3As and $Rh_2(OAc)_4$. This provides a direct, convergent and completely diastereoselective route to this general class of epoxides from readily available reagents. Furthermore, as the conditions are exceptionally mild, (the reaction will tolerate base-, acid- and oxidatively-sensitive

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† Electronic supplementary information (ESI) available: new compounds. See http://www.rsc.org/suppdata/cc/b2/b204252e/

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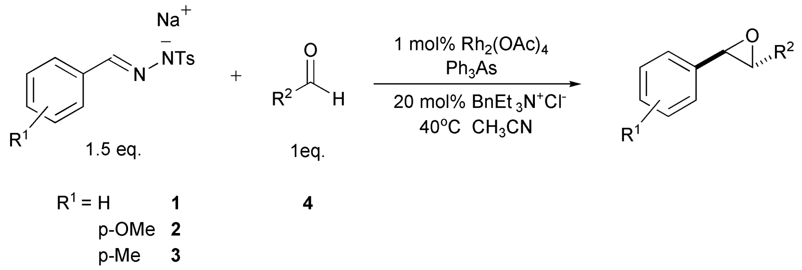
Table 1 Yields and ratios of epoxides and alkenes obtained using aldehyde **4** and aryl tosylhydrazone salts **1**–**3** using triphenylarsine



Entry[a]	Tosylhydrazone salt	Aldehyde (R^2CHO)	Ph_3As/mol%	Yield of epoxide (%)	*Trans*:*cis* selectivity[b]	Yield of alkene (%)
1	**1**	*p*-Chlorobenzaldehyde	100	82	100:0	0[c]
2	**1**	Benzaldehyde	100	89	100:0	0[c]
3	**1**	Valeraldehyde	100	70	> 98:2	8
4	**1**	Isobutyraldehyde	100	53	100:0	13
5	**1**	Cyclohexanecarboxaldehyde	100	77	100:0	12
6	**1**	*p*-Chlorobenzaldehyde	20	70	100:0	0[c]
7	**1**	Benzaldehyde	20	62	100:0	0[c]
8	**1**	Valeraldehyde	20	10	100:0	7
9	**1**	Isobutyraldehyde	20	28	100:0	10
10	**1**	Cyclohexanecarboxaldehyde	20	30	100:0	8
11	**2**	Benzaldehyde	100	92	> 98:2	0
12	**2**	Cyclohexanecarboxaldehyde	100	64	> 98:2	0
13	**2**	Benzaldehyde	20	76	100:0	0
14	**2**	Cyclohexanecarboxaldehyde	20	40	> 98:2	0
15	**3**	Benzaldehyde	100	98	100:0	0
16	**3**	Cyclohexanecarboxaldehyde	100	85	100:0	0[c]
17	**3**	Benzaldehyde	20	93	100:0	0[c]
18	**3**	Cyclohexanecarboxaldehyde	20	42	100:0	0[c]

[a] Ph_3As (20 mol% or 100 mol%), PhCHO (0.33 mmol), CH_3CN (1mL), $Rh_2(OAc)_4$ (1 mol%), benzyltriethylammonium chloride (20 mol%), tosylhydrazone salt (1.5 eq.). [b] Selectivity refers to epoxide geometry. [c] Traces of alkene were observed by NMR analysis.

groups), this convergent and stereoselective reaction will be the method of choice in many instances.

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11 A typical procedure: to a 5 mL round bottomed flask fitted with a nitrogen balloon was added sequentially: triphenylarsine (20 mol% or 100 mol%), anhydrous acetonitrile (1.0 mL), rhodium(II) acetate dimer (1.5 mg, 1 mol%), benzyl triethylammonium chloride (15 mg, 20 mol%), aldehyde **4** (0.33 mmol, 1.0 equiv.) and tosylhydrazone sodium salt **1**–**3** (0.50 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for 10 min, then at 40 °C for 3 h. The reaction was quenched by the addition of water (0.5 mL) and ethyl acetate (0.5 mL). The aqueous layer was washed with ethyl acetate (2 × 0.5 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was analysed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash column chromatography to afford the corresponding epoxide. Note the tosyl hydrazone salt is not soluble in MeCN and the PTC is added to aid its passage from the solid phase to the solution phase, where it fragments to the diazocompound.