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Oxidative rearrangement of alkynes to chiral α-arylalkanoic esters

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Chiral α-arylalkanoic esters, valued as anti-inflammatory agents, are synthesised through an enantioselective oxidative rearrangement of alkynes under green, metal-free conditions. This study achieves this transformation using chiral iodine(III) reagents with *para*-toluenesulfonic acid and various alcohols, producing the esters in up to 91% yield and 99% enantiomeric excess. The scope of the reaction particularly includes electron-rich non-terminal arylalkynes. Density functional theory calculations give insight into the origin of enantioselectivities of this process.

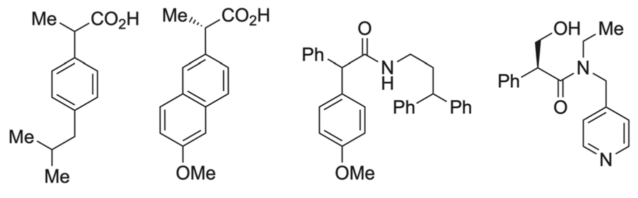
Introduction

The facile generation of cationic species as reactive intermediates in organic synthesis is an area in which hypervalent iodine reagents have proven exceptionally useful. These intermediates can react directly with nucleophiles[1–6] or undergo rearrangements such as aryl migration,[7–9] ring contractions[10–12] or ring expansions.[13,14] Alkenes have long served as precursors in such transformations, as their reaction with iodine(III) reagents readily affords cationic intermediates; ketones have also been employed in related rearrangements.[15,16] Alkynes are likewise known to react with hypervalent iodine compounds to generate alkynyl- or alkenyl-substituted iodine(III) species.[17,18] While these reagents have been primarily used in alkynylations or alkenylations, we report here a distinct approach: the activation of alkynes with iodine(III) reagents to synthesise α-arylalkanoic esters through a rearrangement pathway.

α-Arylalkanoic esters bearing an α-stereogenic centre as precursors of α-arylalkanoic acids are both synthetically challenging and of considerable importance as intermediates and functional motifs in medicinal, pharmaceutical, agrochemical, and natural products chemistry. Representative examples are shown in Fig. 1. Ibuprofen **1** and naproxen **2**, members of the profen family, are widely used non-steroidal anti-inflammatory drugs.[19–21] The α-arylalkanoic acid motif also occurs in the cannabinoid CB_1 receptor ligand **3** [22] and the mydriatic drug tropicamide **4**.[23]

Numerous synthetic strategies for α-arylalkanoic acids and esters have been reported, including Cu-catalysed carboxylation of arylalkenes with CO_2 in the presence of chiral ligands,[19] Pd-catalysed enantioselective Markovnikov hydroxycarbonylation of vinyl arenes with CO and water,[24] Au-catalysed arylation of diazoesters,[25] Tl-catalysed oxidation and 1,2-migration of aryl ketones in alcohol,[26] Ti-catalysed hydromethylation of α-alkene esters,[27] and Ir- and Ru-catalysed α-methylation of aryl esters with methanol as the methylating agent.[28,29] Many of these methods suffer from unfavourable reaction conditions, including the need for moisture and air-free environments, the high cost and toxicity of metals, and the risk of heavy-metal contamination particularly in drug products. Consequently, there has been growing interest in metal-free approaches that operate under milder and more sustainable conditions.

Togo and coworkers developed an oxidative 1,2-aryl migration of aryl ketones **5** to produce α-arylalkanoic esters **6** using hypervalent iodine reagents,[15] and our group subsequently extended this approach to enantioselective synthesis using



1 (Ibuprofen) **2** (Naproxen) **3** (CB_1 receptor ligand) **4** (Tropicamide)

Fig. 1 Drug molecules with α-arylalkanoic acid motif.

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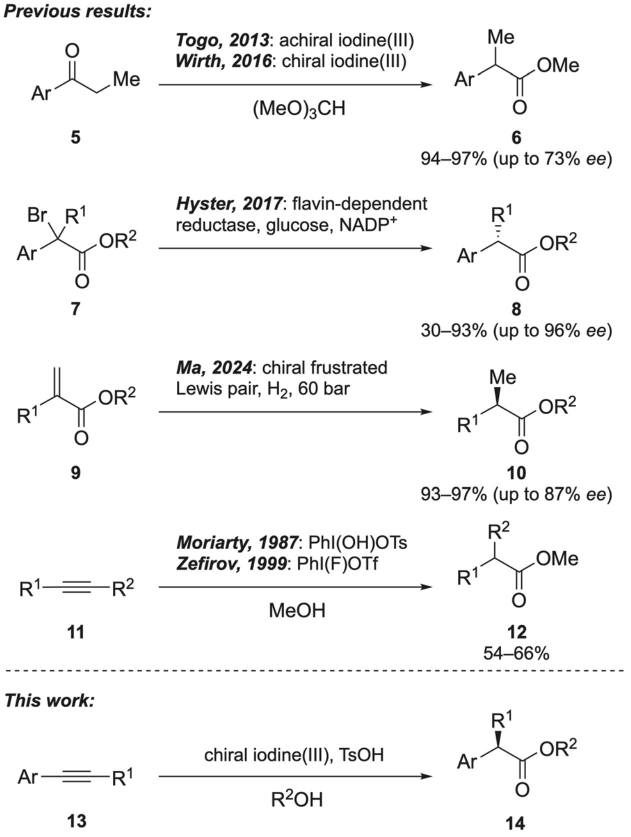


Fig. 2 Metal-free strategies for the synthesis of α-arylalkanoic esters.

chiral iodine(III) reagents, affording products **6** with up to 73% *ee* (Fig. 2a).[15] Hyster and coworkers reported a new methodology for preparing chiral α-arylalkanoic esters **8** through debromination of racemic α-bromoesters **7** using flavoenzymes and glucose in the presence of NADP$^+$ (Fig. 2b).[30] More recently, Ma and coworkers developed a metal-free hydrogenation of α,β-unsaturated esters **9** to synthesise chiral α-arylalkanoic esters **10** using chiral frustrated Lewis pairs under a hydrogen atmosphere (Fig. 2c).[31] To date, only two protocols for the synthesis of α-arylalkanoic esters from alkynes with iodine(III) reagents have been reported. In 1987, Moriarty and coworkers used Koser's reagent [PhI(OH)OTs] for the oxidative rearrangement of alkynes **11** to esters **12** in methanol at reflux for extensive times (Fig. 2d).[32] In 1999, Zefirov *et al.* used a different hypervalent iodine reagent [PhI(F)OTf] for the same reaction.[33] Given these reported procedures, there is a clear need for a clean and environmentally benign process to produce α-arylalkanoic esters and hypervalent iodine chemistry presents a promising solution. In this work, we establish highly selective, metal-free conditions for the oxidative rearrangement of electron-rich alkynes **13**, enabling the efficient synthesis of both chiral and racemic α-arylalkanoic esters **14** by using simply prepared, recyclable hypervalent iodine reagents.

Results and discussion

For our initial investigation, 1-methoxy-4-(prop-1-yn-1-yl)benzene **15** was selected as a model substrate owing to its electron-rich aryl group. [Bis(trifluoroacetoxy)iodo]benzene was used as a strong oxidant for the reaction; however, only minimal decomposition of the starting material **15** was observed after 20 h at room temperature (Table 1, entry 1).

1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) is known as a highly polar, low-nucleophilicity solvent capable of stabilising charged intermediates in solution. It has been successfully employed to promote challenging transformations, including alkyne cleavage and oxidative rearrangements of alkenes.[34–36]

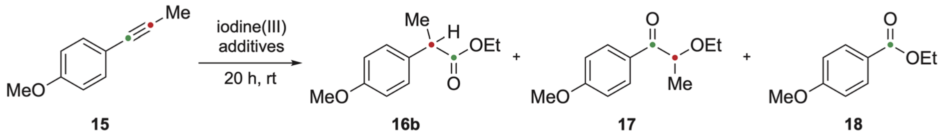
When a mixture of HFIP and 8 equivalents of ethanol was used in combination with Koser's reagent, only trace amounts of the rearranged product **16b** were obtained, accompanied by the formation of ester **18** (Table 1, entry 2). As an oxidative cleavage of triple bonds with iodine(III) reagents has already been reported,[37] the generation of the product **18** was not unexpected.

To further improve the conditions for promoting the formation of the desired product, 3 equivalents of hydrated *para*-toluenesulfonic acid were added to the reaction mixture, yielding 13% of product **16b** (Table 1, entry 3). When ethanol was used as a solvent with anhydrous *para*-toluenesulfonic acid, the conversion reached 100%, however, with the formation of **17** as the main product (Table 1, entry 7). The synthesis of 1,2-diketones and α-hydroxyketones from alkynes with iodine(III) reagents has been reported,[38,39] which explains its presence in the mixture. Application of boron trifluoride etherate had a distinct effect in generating compound **16b** (Table 1, entry 8), nevertheless after further optimisation (see supporting information), the use of 1.5 equivalents of (diacetoxyiodo)benzene and anhydrous *para*-toluenesulfonic acid were found to provide **16b** in yields up to 90% (Table 1, entry 9). Further optimisation details are in the SI (Tables S1–S4).

With these optimised conditions for the oxidative rearrangement, a series of chiral hypervalent iodine reagents, illustrated in Table 2, were synthesised and screened to access chiral α-arylalkanoic esters. The enantioselective oxidative rearrangement of alkynes was achieved under similar reaction conditions, simply by replacing (diacetoxyiodo)benzene with chiral iodine(III) reagents **19** (Table 2).

Chiral hypervalent iodine reagents with alkyl lactates such as methyl (**19a**), ethyl (**19b**), and isopropyl (**19c**) produced (*R*)-**16b** in low enantioselectivities (~30% *ee*) (Table 2, entries 1–3). Replacing alkyl esters with sterically more demanding chiral alkyl esters, such as L-menthyl (**19d**), decreased the enantiomeric excess to 21%. Iodine reagents with amide moieties were investigated because of the potential interactions between the NH hydrogen atom and the oxygen of the acetate ligands on iodine, which could enhance the chiral environment around the iodine centre, leading to higher enantiomeric excess of the desired product.[40] Indeed, presence of the tosyl amide moiety (**19e**) increased the enantiomeric excess to 40% (Table 2, entry 5), and arylamides with electron-withdrawing groups such as **19f** and **19g** furnished (*R*)-**16b** in almost racemic form (Table 2, entries 6 and 7). In contrast, amides bearing aryl or alkyl substituents (**19h**–**19j**), increased the enantiomeric excess of (*R*)-**16b** significantly to 76%, 79% and 85%, respectively (Table 2, entries 8–10). These results clearly indicate that amide

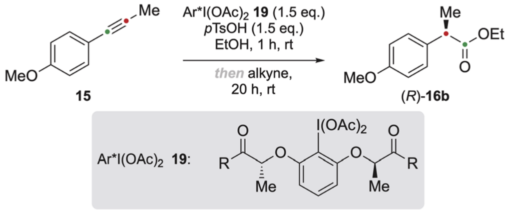
Table 1 Optimisation of the oxidative rearrangement of alkyne **15**



Entry	Iodine(III) reagent	Additives	Solvent	Conversion[a] [%]	**16b** yield[b] [%]	**17** yield[b] [%]	**18** yield[b] [%]
1	3 eq. $PhI(OCOCF_3)_2$[c]	—	EtOH	10	0	0	0
2	3 eq. PhI(OH)O*p*Ts	—	HFIP/EtOH (8 eq.)	40	Trace	0	15
3	3 eq. PhI(OH)O*p*Ts	3 eq. *p*TsOH·H_2O	HFIP/EtOH (8 eq.)	68	13	0	16
4	3 eq. $PhI(OAc)_2$	3 eq. *p*TsOH·H_2O	HFIP/EtOH (8 eq.)	72	15	0	Trace
5	3 eq. $PhI(OCOCF_3)_2$	3 eq. *p*TsOH anh.	HFIP/EtOH (8 eq.)	75	25	0	0
6	3 eq. $PhI(OCOCF_3)_2$	3 eq. *p*TsOH anh.	HFIP/EtOH (30 eq.)	80	37	0	0
7[d]	3 eq. $PhI(OCOCF_3)_2$	3 eq. *p*TsOH anh.	EtOH	100	20	53 (47)[e]	0
8	3 eq. $PhI(OCOCF_3)_2$	3 eq. *p*TsOH anh., 3 eq. BF_3·OEt	EtOH	91	64 (61)[e]	0	0
9	1.5 eq. $PhI(OAc)_2$	1.5 eq. *p*TsOH anh.	EtOH	100	(90)[e]	0	0

[a] Based on re-isolated **15**. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] Similar results were obtained with PhI(OH)OTs and $PhI(OAc)_2$ (see SI, Table S2). [d] Reaction time: 40 h. [e] Amount in brackets: isolated yield.

Table 2 Screening of chiral hypervalent iodine reagents for the enantioselective synthesis of **16b**



Entry	Iodine(III) reagent	R	(*R*)-**16b** yield[a] [%]	(*R*)-**16b** *ee*[b] [%]
1	**19a**	OMe	90	30
2	**19b**	OEt	89	30
3	**19c**	O*i*Pr	88	32
4	**19d**	*O*-L-menthyl	85	21
5	**19e**	NH*p*Ts	82	40
6	**19f**	NHC_6F_5	81	8
7	**19g**	$NH[3,5-(CF_3)_2–C_6H_3]$	88	0
8	**19h**	NH[2,6-(*i*Pr)$_2$-C_6H_3]	82	76
9	**19i**	NH[(*R*)-CH(Me)Ph]	80	79
10	**19j**	NH[(*S*)–CH(Me)Ph]	83	85

[a] Isolated yields. [b] Determined by HPLC.

substituents play a significant role in the observed enantioselectivities of this transformation. Reagent **19j** showed the best results, forming (*R*)-**16b** in 83% yield and with 85% *ee* (Table 2, entry 10), and thus was selected and applied to the stereoselective synthesis of the products shown in Fig. 3.

To investigate the applicability of this reaction in the formation of esters of different alcohols, methanol (**16a**), ethanol (**16b**), *n*-propanol and *iso*-propanol (**16c**, **16d**) were used as solvents. While the yields for the methyl and ethyl esters were rather satisfying, 87% and 90% respectively, the yields for the *n*-propyl and *iso*-propyl esters were noticeably lower, 78% and 46% respectively, even after application of boron trifluoride etherate. The addition of this Lewis acid was proven to be beneficial for the formation of methyl and *iso*-propyl esters **20**, **21**, **22** and **24** (see Fig. 3 and SI for details).

Neither the introduction of a methyl group in the *meta*-position relative to the alkyne nor the relocation of the methoxy substituent from *para* to *ortho* significantly influenced the reaction efficiency; in both cases, products **20** and **21** were obtained in excellent yields of up to 90%. 2,4-Dimethoxy-substituted alkynes subjected to the reaction conditions at 25 °C remained unreactive and could be recovered without any

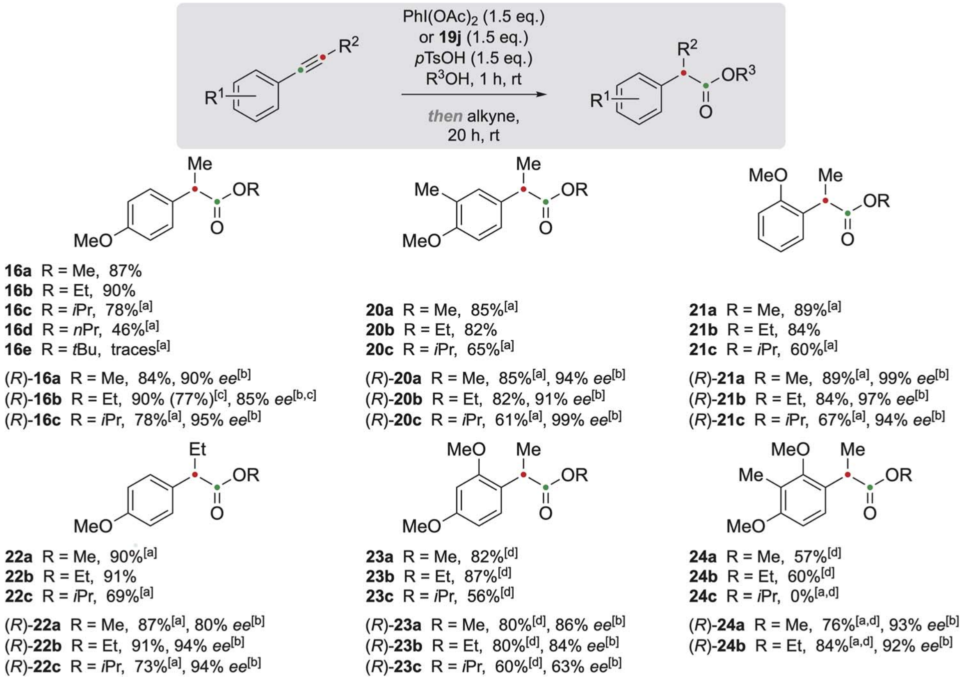


Fig. 3 Scope of the alkyne rearrangement. [a] $BF_3\cdot OEt_2$ (1.5 eq.) was added after the addition of the alkyne. [b] Determined by HPLC. [c] Scale-up: **19j** (10.26 mmol, 7.23 g), anh. pTsOH (10.26 mmol, 1.77 g) in EtOH (20 mL) for 1 h, then 15 (6.84 mmol, 1.00 g) at 25 °C, 20 h. [d] The reaction was carried out at 45 °C.

noticeable decomposition, which necessitated a temperature increase to 45 °C. The temperature increase led to the formation of products **23** and **24** in 56–87% yield except for the *iso*-propyl ester **24**, which was not obtained. An exchange of the methoxy-substituent in **15** to a dimethylamino moiety did not lead to a successful reaction and only 4-dimethylamino benzoic esters were formed. Several other alkynes (see SI, page S19) were also unreactive under the reaction conditions.

The yields of the chiral α-arylalkanoic esters were similar to those of the racemic ones. Alkynes bearing electron-donating groups were successfully oxidised, producing the rearranged products in high enantiomeric excesses of 80–99% (see Fig. 3, compounds (*R*)-**16**, **20–24**), except for product (*R*)-**23c** which was obtained in a lower enantiomeric excess of 63%. The reaction conditions seem to be very selective to non-terminal alkynes bearing electron-donating substituents in *ortho*- or *para*-positions. When arylalkynes with electron-withdrawing groups were subjected to the reaction conditions, they were completely recovered.

With a wide scope of esters produced, further investigation was conducted to study the applicability of this method for performing this oxidative rearrangement on a larger scale. The reaction was scaled up using alkyne **15** on a gram scale. The reaction with **19j** performed smoothly, delivering the desired chiral product (*R*)-**16b** in 77% yield (1.09 g) with identical enantioselectivity as on the small scale (85% *ee*) (Fig. 3, compound (*R*)-**16b**, values in brackets).

We also demonstrated that the reduced chiral iodoarene can be easily recovered in almost quantitative yield and re-oxidised to the hypervalent iodine reagent **19j** for reuse. The recycled reagent showed identical results (on a small-scale reaction) without any loss of activity and selectivity, forming product (*R*)-**16b** in 90% yield and with 85% *ee*.

The development of a process using only catalytic amounts of an iodine(I) reagent and a stoichiometric oxidant was unsuccessful, as some oxidants did not provide sufficient reactivity (Oxone®, sodium perborate) while others directly reacted with the alkyne (Selectfluor®, *m*CPBA).

In addition, the methodology was used to prepare naproxen **2** (Fig. 4). Naproxen **2** is a well-known anti-inflammatory drug, but can also be applied as a chiral discriminating reagent in NMR spectroscopy.[41] The alkyne **25** was synthesised using the Corey–Fuchs methodology from the corresponding aldehyde and converted with (diacetoxyiodo)benzene in ethanol to naproxen ethyl ester *rac*-**26** in 48% yield. The use of *ent*-**19i** provided (*S*)-**26** in 88% *ee*, which was hydrolysed to the biologically active compound (*S*)-**2** in 30% overall yield.

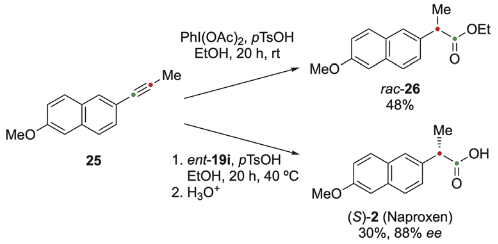


Fig. 4 Stereoselective synthesis of Naproxen (*S*)-**2**. Compound *ent*-**19i** [(2,6-bis(((*S*)-1-oxo-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)oxy)phenyl)-l^3-iodanediyl diacetate] is the enantiomer of **19i**.

To gain deeper insight into the origin of enantioselectivity, density functional theory (DFT) calculations were performed at the B3LYP-D4/def2-TZVP//B3LYP-D4/def2-SVP/CPCM(ethanol) level of theory. The oxidative rearrangement of substrate **15** to (*R*)-**16b** was chosen as a model substrate for mechanistic investigation. In agreement with literature precedence,[32,33] the proposed mechanism is outlined in Fig. 5.

The reaction sequence begins with *para*-toluene sulfonic acid (*p*TsOH) reacting with the chiral (diacetoxyiodo)arene (**INT-1**), releasing acetic acid through ligand exchange and generating the active iodine(III) species **INT-2**. Insertion of alkyne **15** into the I–OTs bond affords **INT-3**. Subsequent displacement of the tosylate by ethanol and further ligand exchange at iodine(III) produces the more stable vinyl iodonium intermediate **INT-4**.

The enantiodetermining step is proposed to be the protonation of **INT-4** at the α-carbon by the previously released acetic acid, thereby establishing the stereogenic centre and forming the carbocationic intermediate **INT-5**. Nucleophilic attack by acetate at the β-carbon atom of **INT-5** then produces the unstable alkyl iodonium species **INT-6**. This intermediate undergoes rapid 1,2-aryl migration through an S_N2 displacement of the iodoarene and elimination of the tosylate, providing the principal driving force for the transformation. The resulting species **INT-7** reacts with ethanol to yield *ortho*-ester **INT-8**, which hydrolyses under the reaction conditions to give (*R*)-**16b**.

This reaction sequence highlights the electronic demand of this reaction: resonance stabilisation by the methoxy group in **INT-4** lowers the activation barrier for enantioselective protonation in electron-rich arylalkynes. Consequently, analogous substrates with $-CF_3$ substituents face prohibitively high barriers to protonation by acetic acid, in agreement with experimental results (see SI, Fig. S4).

To rationalise the origin of enantioselectivity, we investigated the enantiodetermining protonation step in detail and the subsequent 1,2-aryl migration. The computed energy profiles for the competing pathways leading to the (*R*)- and (*S*)-enantiomers are presented in Fig. 6. The stepwise addition of acetic acid to **INT-4** constitutes the enantiodetermining step of the reaction. Conformational analysis revealed that the ground-state conformer of **INT-4**, in which the *si*-face is accessible for protonation is favoured by 1.1 kcal mol^{-1} over the conformer exposing the re-side (see SI, Fig. S1 and S2). Intramolecular hydrogen-bonding interactions rigidify the chiral backbone of **INT-4**. Exposure of the re-side necessitates a rearrangement of the chiral backbone while keeping hydrogen-bonding interactions intact, resulting in an overall unfavoured geometry. This

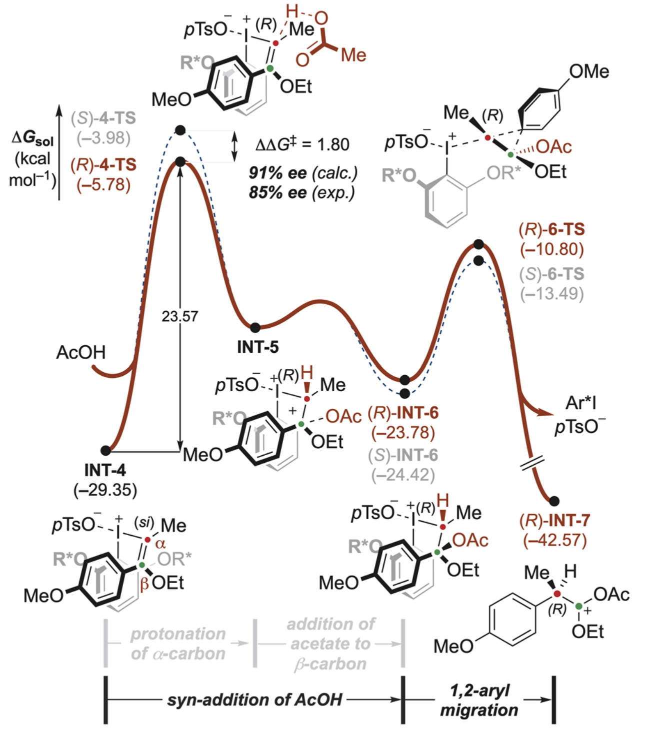


Fig. 6 DFT calculated energy profiles for competing protonation of INT-4 by acetic acid.

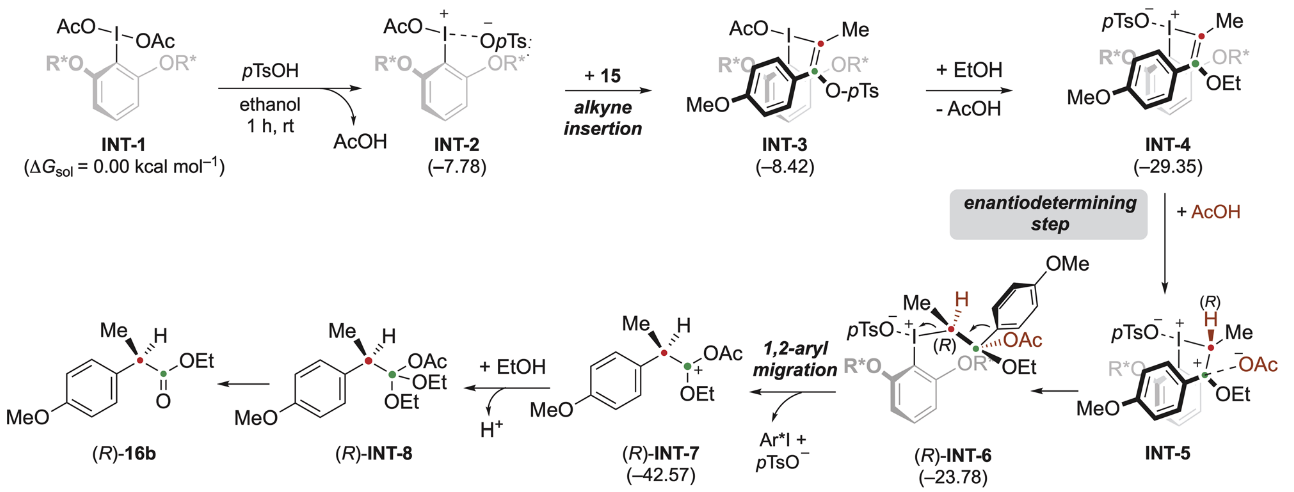


Fig. 5 Proposed reaction mechanism. Gibbs free energies in solution are given (in kcal mol^{-1}) in parentheses underneath the structure numbers.

conformational bias is reflected in the computed barrier heights for protonation: the transition state leading to the (*R*)-enantiomer, (*R*)-**4-TS**, is 1.8 kcal mol^{-1} more favourable than (*S*)-**4-TS**. The corresponding difference in barriers predicts an *ee* of 91%, in excellent agreement with the experimentally observed value of 85% (see Fig. 6). The subsequent 1,2-aryl migration and elimination of iodine(III) fragment occur rapidly and irreversibly, confirming that protonation of **INT-4** is the enantio-determining event in this transformation.

Conclusions

This work highlights a significant breakthrough in the enantioselective oxidative rearrangement of alkynes, enabling a highly efficient synthesis of chiral α-arylalkanoic esters under straightforward, green, and metal-free conditions. The process employs iodine(III) reagents and *para*-toluenesulfonic acid, affording high yields across a broad range of alcohols within 20 hours. The method exhibits excellent selectivity for electron-rich, non-terminal alkynes. Novel sterically hindered alkynes were also synthesised, expanding the scope of accessible α-arylalkanoic esters. Screening of chiral C_2-hypervalent iodine reagents identified an amide side chain as being most efficient, achieving up to 91% yield and up to 99% enantiomeric excess. The reaction was successfully scaled for practical applications. The synthesis of the drug naproxen was demonstrated alongside the recyclability of the chiral iodoarene adding to its environmental appeal.

Experimental

General procedure for the oxidative rearrangement of alkynes

In a 10 mL dried finger vial or round bottom flask and under nitrogen atmosphere, (diacetoxyiodo)arene (1.5 mmol, 1.5 eq.) and anhydrous *p*TsOH (1.5 mmol, 1.5 eq.) were dissolved in 1 mL of alcohol and stirred for one hour at room temperature followed by the addition of alkyne substrate (1 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure. The residue was dissolved again with ethyl acetate and washed with sat. aq. $NaHCO_3$ (10 mL) solution and sat. aq. $Na_2S_2O_3$ solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ (15 g), filtered, and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate: 97 : 3).

Author contributions

T. W. conceptualised the work. R. A. developed the methodology. R. A., H. G., M. F., J. L. M, D. and D. B. performed all the experiments and analysed the data. J. W., A. G., R. B. and M.-H. B. performed and analysed the calculations. R. A., J. W., M.-H. B., R. L. M. and T. W. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): experimental details, characterisation data, additional discussions, DFT optimised geometries, energies and frequencies. See DOI: **https://doi.org/10.1039/d5sc07882b**.

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