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Palladium-catalysed regio- and stereoselective arylative substitution of γ,δ-epoxy-α,β-unsaturated esters and amides by sodium tetraaryl borates†

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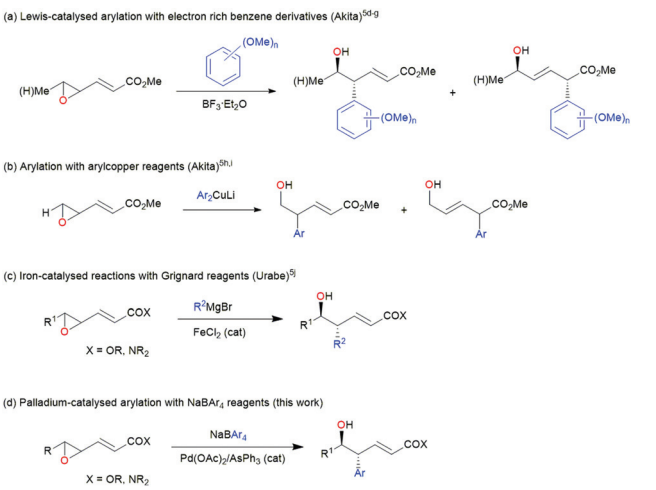
Palladium-catalysed reactions of γ,δ-epoxy-α,β-unsaturated esters and amides with $NaBAr_4$ reagents proceeded regio- and stereoselectively, producing allylic homoallyl alcohols with aryl-substituents in the allylic position for a wide range of substrates. $AsPh_3$ was found to be a competent ligand for the arylation reaction, whereas phosphine ligand/Lewis acidic organoboron combinations favoured the substitution reaction by oxygen nucleophiles (*e.g.* H_2O, ROH).

Introduction

Stereoselective ring opening reactions of epoxides constitute one of the most important methods in organic chemistry.[1] Specifically, epoxy-functionalized acrylic acid derivatives are versatile reagents in epoxide ring-opening substitution reactions with oxygen,[2] nitrogen,[3] hydride,[4] and carbon-centered[5,6] nucleophiles, which mainly take place in the form of 1,2-addition (S_N2).

To date, arylative ring-opening reactions of γ,δ-epoxy-α,β-unsaturated carboxylic acid derivatives have been possible using methods involving π-electron-rich aromatics in the presence of a Lewis acid catalyst (Scheme 1a),[5d–g] arylcoppers (Scheme 1b),[5h,i] or Grignard reagents in the presence of an iron catalyst (Scheme 1c).[5j] The first two methods usually suffer from occasionally low regioselectivity or unsatisfactory yields. Furthermore, any method using hard organometal nucleophiles, such as organocopper or Grignard reagents, requires an absolutely moisture-free environment and has low functional group tolerance. Nevertheless, soft arylborons are generally preferable reagents for C–C bond formation because of their low toxicity, availability, high functional group tolerance, longer shelf lives, and moisture insensitivity.[7]

Interestingly, to the best of our knowledge, there is no reported method in the literature utilizing arylboron reagents in the C–C bond formation of epoxy acrylic acid derivatives, except for those methods involving simple vinyl epoxides[8] and styrenyl epoxides,[9] wherein the reactions took place by 1,4-addition (S_N2') and α–aryl substitution, respectively. Perhaps, the most important reason for this is that exposure of the π-allylpalladium, a putative intermediate in palladium-catalysed reactions of allylic reagents, to the Lewis acidic boron-promoted attack of oxygen nucleophiles, which may be present in the form of boronic acid, water, or alcohol additives.[2] Nevertheless, herein, we demonstrate that stereoselective S_N2-type arylation of γ,δ-epoxy-α,β-unsaturated carboxylic acid derivatives can be successfully performed by the use of $NaBAr_4$ as the non-acidic organoboron reagent and $AsPh_3$ ligand under palladium catalysis (Scheme 1d).



Scheme 1 Previous studies on the arylation of γ,δ-epoxy-α,β-unsaturated carboxylic acid derivatives.

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†Electronic supplementary information (ESI) available: General procedures, tables for optimisation studies and robustness screening data, spectroscopic data for new compounds. See DOI: 10.1039/d0ob01226b

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Results and discussion

As the first attempt, the reaction of ester-functionalized vinyl epoxide **1a** and PhBneop was carried out at room temperature (rt), in the presence of $(i\text{-Pr})_2NH$ base and the $Pd_2(dba)_3$-$CHCl_3/PPh_3$ (P/Pd = 4.1 : 1) catalyst combination, in a THF/water (4 : 1) mixture, in a Schlenk flask, and under Ar gas. In line with the reactivity trend mentioned above, this reaction proceeded with complete conversion, producing a vicinal diol, structure **4a**, in exclusively the *syn*-configuration as the major product, albeit formed in low yield (Table 1, entry 1).[10] No detectable amount of any arylated product could be detected to form by GC/MS and ^{1}H-NMR techniques.

Numerous electron-rich and poor monodentate, as well as bidentate ligands were screened in the reaction (see the ESI†). Generally, phosphine ligands favoured the formation of **4a**, among which dppe provided the highest yield of **4a** (entry 2). In the presence of dppe, a non-acidic borate reagent, $NaBPh_4$, was also tried, but a complex mixture formed as a result of the reaction (entry 3).

Nevertheless, it was intriguing to find that the use of a more labile ligand, such as $AsPh_3$, for the reaction of **1a** and PhBneop rendered the arylative ring-opening reaction from the allylic position, thereby leading to γ-aryl-substituted homoallyl alcohols **3aa** in a moderate yield with almost clean stereoselectivity,[11] and no trace of **4a** was detected (entry 4). It is apparent that the presence of a ligand is essential for the reaction because no conversion occurred under a ligand-free conditions (entry 5).

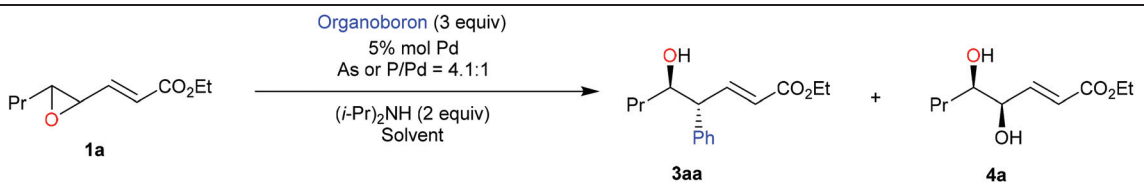
Substitution of water with MeOH co-solvent resulted in considerable acceleration of the reaction at 50 °C (entries 6 and 7). Contrary to the result obtained under the conditions of entry 3, a good yield of **3aa** was obtained by using $NaBPh_4$ (**2a**) instead of PhBneop under the conditions of entry 8;[12] however, the presence of a base is required for a reasonable yield (entry 9). Gradual increments in the yield were observed using 1,4-dioxane, $Pd(OAc)_2$, and elevated reaction temperatures (entries 10–12).

To maintain volatile MeOH and $(i\text{-Pr})_2NH$ in solution with high proportion, all reactions at ≥70 °C were carried out in a sealed Schlenk tube. The reaction was incredibly fast at 110 °C, completed within just 2 minutes, as judged by the appearance of palladium black (entry 13). The amount of **2a** could be reduced to 2 equivalents without sacrificing the yield (entry 14).[13] On the other hand, reducing the amount of palladium catalyst resulted in a lower yield of the product (entry 15).

Having established effective conditions, an array of vinyl epoxide substrates was then subjected to the reactions with a number of $NaBAr_4$ reagents and the related results are listed in Table 2. When reacted with **2a**, high yields of homoallyl alcohols were able to be achieved with epoxy alkenyl ester substrates having a *primary* alkyl-substituted and *trans*-configured epoxy moiety, regardless of the structure of the ester group (entries 1–3).

The relative stereoisomeric configuration of homoallyl alcohol **3da** was decidedly verified by NOE interaction studies and the ^{1}H-NMR coupling constant (10 Hz) of the vicinal *ter-*

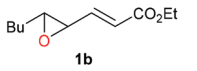
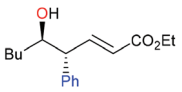
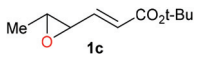
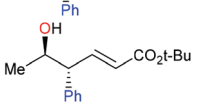
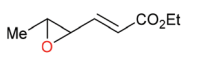
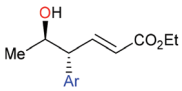
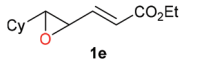
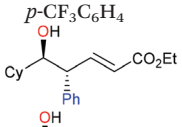
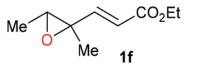
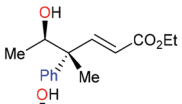
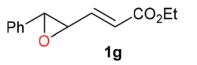
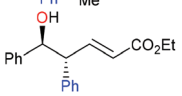
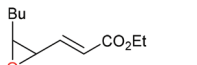
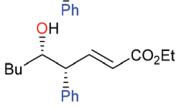
Table 1 Reaction optimization with vinyl epoxide **1a**[a]



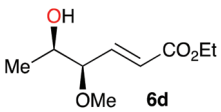
Entry	Organoboron	Pd/ligand	Solvent (mL)	T (°C)	Time	Yield[b] %
1	PhBneop	$Pd_2(dba)_3$-$CHCl_3/PPh_3$	THF/H_2O (4 : 1)	Rt	45 min	34 **4a**
2	PhBneop	$Pd_2(dba)_3$-$CHCl_3$/dppe	THF/H_2O (4 : 1)	Rt	O.N.	77 (69)[c] **4a**
3	$NaBPh_4$	$Pd_2(dba)_3$-$CHCl_3$/dppe	THF/H_2O (4 : 1)	Rt	O.N.	N.D.
4	PhBneop	$Pd_2(dba)_3$-$CHCl_3/AsPh_3$	THF/H_2O (4 : 0.5)	Rt	48 h	55 **3aa**
5	PhBneop	$Pd_2(dba)_3$-$CHCl_3$	THF/H_2O (4 : 0.5)	Rt	48 h	N.C.
6	PhBneop	$Pd_2(dba)_3$-$CHCl_3/AsPh_3$	THF/H_2O (4 : 0.5)	50	O.N.	55 **3aa**
7	PhBneop	$Pd_2(dba)_3$-$CHCl_3/AsPh_3$	THF/MeOH (4 : 0.5)	50	3 h	55 **3aa**
8	$NaBPh_4$	$Pd_2(dba)_3$-$CHCl_3/AsPh_3$	THF/MeOH (4 : 0.5)	50	3.5 h	76 **3aa**
9[d]	$NaBPh_4$	$Pd_2(dba)_3$-$CHCl_3/AsPh_3$	THF/MeOH (4 : 0.5)	50	5 h	48 **3aa**
10	$NaBPh_4$	$Pd(OAc)_2/AsPh_3$	THF/MeOH (4 : 0.5)	50	4 h	78 **3aa**
11	$NaBPh_4$	$Pd(OAc)_2/AsPh_3$	THF/MeOH (4 : 0.5)	70	1 h	82 **3aa**
12	$NaBPh_4$	$Pd(OAc)_2/AsPh_3$	dioxane/MeOH (4 : 0.5)	70	40 min	85 **3aa**
13	**$NaBPh_4$**	**$Pd(OAc)_2/AsPh_3$**	**dioxane/MeOH (4 : 0.5)**	110	2 min	**90 (87) 3aa**
14	**$NaBPh_4$**[e]	**$Pd(OAc)_2/AsPh_3$**	**dioxane/MeOH (4 : 0.5)**	110	2.5 min	**90 3aa**
15	$NaBPh_4$[e]	$Pd(OAc)_2/AsPh_3$[f]	dioxane/MeOH (4 : 0.5)	110	4 min	50 **3aa**

[a] Epoxide **1a**: 0.2 mmol; Phneop: phenylboronic acid neopentylglycol ester; N.D.: not determined; N.C.: no conversion; dppe: 1,2-bis(diphenylphosphino)ethane. [b] Determined by ^{1}H-NMR using benzaldehyde as the internal standard. [c] Isolated yield. [d] Without added base. [e] 2.0 equiv. [f] 1.0% Pd.

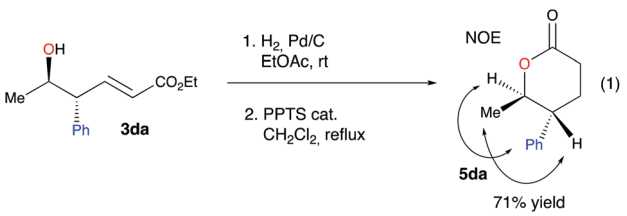
Table 2 Allylic arylation of γ,δ-epoxy-α,β-unsaturated esters with $NaBAr_4$ reagents[a]

Entry	Epoxide	Product		Yield %
1	 **1b**		**3ba**	89
2	 **1c**		**3ca**	82
	 **1d**			
3		Ar: Ph	**3da**	90
4		*p*-Me-C_6H_4	**3db**	79
5		*m*-$MeOC_6H_4$	**3dc**	81
6		*m*-FC_6H_4	**3dd**	87
7		*p*-$CF_3C_6H_4$	**3de**	72[b]
8	 **1e**		**3ea**	67
9	 **1f**		**3fa**	56[c]
10	 **1g**		**3ga**	N.D.
11	 **1h**		**3ha**	50[d]

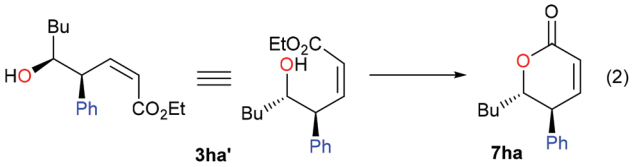
[a] The reaction conditions of entry 14 in Table 1 were applied in the reactions. The reactions were complete within 2–5 minutes. [b] The reaction also gave rise to an allylic methoxylated product (**6d**, 12%). [c] dr = 89 : 11. [d] The reaction also gave rise to a phenyl-substituted unsaturated lactone (**7ha**, 32%).


6d

tiary hydrogen signals of its δ-lactone derivative (eqn (1)); these data clearly indicated that **3da** possessed 4,5-*anti*-configuration[5c,f,j,14]


(1)

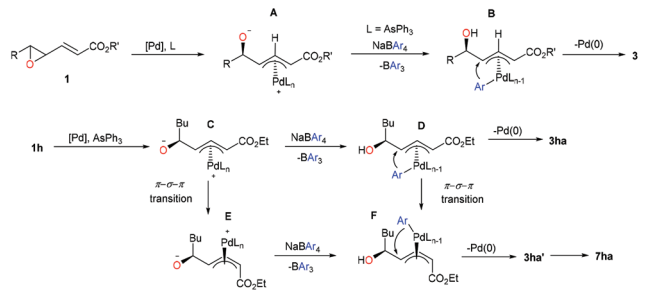
This protocol was also be successfully implemented on $NaBAr_4$ reagents having electron-rich or moderately electron-poor phenyl groups (entries 4–6). The desired arylated product **3de**, was also be obtained in a good yield (72%) from the reaction of **1d** and the highly electron deficient $NaB(p\text{-}CF_3C_6H_4)_4$ (**2e**) reagent. However, its formation was accompanied by an amount of methoxylated side product **6d** (entry 7).[15]


(2)

The reaction of the substrate **1e**, containing a cyclohexyl group on the epoxy terminus, and **2a** led to a relatively lower yield (**3ea**). This result may imply that the method is sensitive to sterical effects at the epoxy site for ester compounds (entry 8). Moreover, when the epoxy group is tri-substituted, the reaction proceeded with a lower level of stereoselectivity (dr = 89 : 11), and furnished the homoallyl product **3fa** in a moderate yield (entry 9). Aryl-substituted substrates do not appear to be suitable for the method; the reaction of the epoxy ester **1g** led to an intricate mixture (entry 10).

It was surprising that the reaction of the substrate **1h**, having a *cis*-configured epoxy moiety, gave rise to an unsaturated lactone product, **7ha**, with *trans*-configuration in a reasonable yield, along with the expected homoallyl product **3ha**, which is the diastereomer of **3ba**. The formation of **7ha** requires a homoallyl structure, **3ha′**, with *Z*- and *anti*-4,5-configurations (eqn (2)), because the inherent structures of all the *E*-configured **3** structures do not allow the hydroxyl and ester groups to provide sufficient distance to undergo cyclative condensation.

The reaction mechanism should be similar to its iron-catalysed counterpart using Grignard reagents as the nucleophilic source (Scheme 1c).[5j] The reaction cycle should begin with ring-opening by the attack of a palladium complex to **1** in *anti*-mode, leading to the formation of π-allylpalladium complex **A** (Scheme 2).[16] Then, in the case where the ligand is $AsPh_3$, sequential transmetalation (**B**) and reductive elimination steps should furnish the arylated homoallyl alcohol structure **3**. The formation of **6d** from the reaction of **1d** and **2e**, even in the presence of $AsPh_3$ (Table 2, entry 7), could be ascribed to the lower transmetalation activity of highly electron deficient **2e** with **A**. At this stage, probably with a promotive effect of the by-product BPh_3 after reaching a critical concentration, **A** was exposed, to some extent, to nucleophilic attack by MeOH.[2,3]

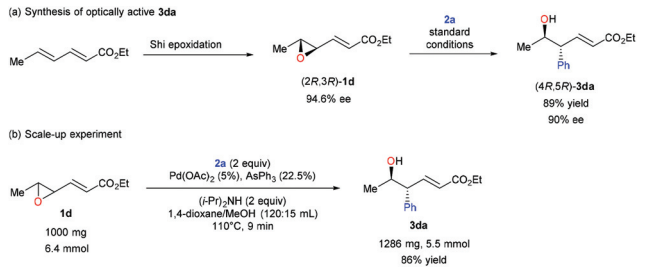

Scheme 2 General reaction mechanisms.

It has been previously shown that $AsPh_3$ is an activating palladium ligand that is superior to the most phophines in accelerating the rate determining transmetalation step in the Stille coupling reaction.[17] Consistent with this finding, it seems that the transmetalation step was the preferred pathway in the presence of the softer ligand, $AsPh_3$, whereas the presence of the more strongly coordinating dppe ligand probably led to a deceleration of the transmetalation step. In turn, **A** was more exposed to nucleophilic oxygen attack in the presence of a Lewis acidic boron compound.

The formation of **3ha′**, which is presumed to be an intermediate structure for the formation of cyclic unsaturated lactone **7ha**, should necessitate π-allylpalladium intermediates **E** or **F**, in which planar allyl ligands bear ester groups oriented *anti* with respect to the middle allylic C–H bond. Further, since the reaction of **1h**, under the standard conditions, primarily yields π-allylpalladium intermediates **C** and **D**, with ester groups oriented *syn*, the formation of **C** or **D** should be followed by a π–σ–π interconversion. For the underlying reasons, it is difficult for us to explain this configurational transition at this time.

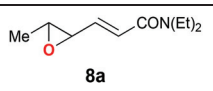
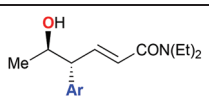
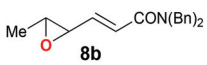
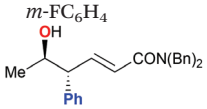
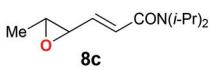
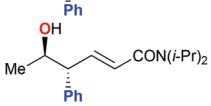
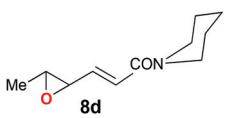
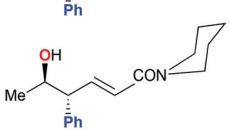
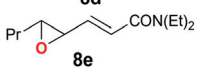
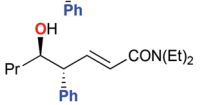
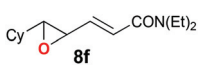
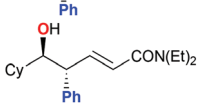
The versatility of this protocol has been further demonstrated by the reaction of an optically active ester reagent and a scale-up experiment. The asymmetric epoxidation of the corresponding diene ester by Shi's method and subsequent reaction of the produced epoxide (2*R*,3*R*)–**1d** and **2a** under standard conditions afforded (4*R*,5*R*)–**3da** with a high level of ee%, which proves that, combined with the Shi's procedure,[18] the present method would be a convenient strategy for the synthesis of optically active aryl-functionalized homoallyl compounds (Scheme 3a).[19] The method was also successfully applied on a gram scale (Scheme 3b); the reaction of 1.00 g of **1b** with 2 equivalents of **2a** was complete within 9 minutes, providing the desired product, **3da**, in a yield comparable to the counterpart mg scale reaction.

Finally, a robustness screen, which was formulized by Glorius and co-workers,[20] was performed with 9 different functional group additives (1 equivalent), including aldehyde, terminal alkyne, terminal alkene, primary alcohol, primary alkyl chloride, phenyl chloride, nitrile, and aniline (see ESI†), to the optimized conditions though it should be qualified that these results only precisely diagnose intermolecular competitions. Subsequently, we followed the yield of **3da** and recovery of the additive. While the protocol generally well-tolerated these additives in terms of **3da** formation, more or less reduction in additive recovery was observed.



Scheme 3 Synthesis of an optically active product and scale-up experiment.

Table 3 Allylic arylation of γ,δ-epoxy-α,β-unsaturated amides (**8**) with $NaBAr_4$ (**2**) reagents[a]

Entry	Epoxide	Product		Yield %
	 **8a**			
1		Ar: Ph	**9aa**	90
2		*p*-Me-C_6H_4	**9ab**	79
3		*m*-FC_6H_4	**9ad**	87
4	 **8b**		**9ba**	92
5	 **8c**		**9ca**	73
6	 **8d**		**9da**	88
7	 **8e**		**9ea**	86
8	 **8f**		**9fa**	91

[a] The reaction conditions of entry 14 in Table 1 were applied, but with 1.5 equivalent of **2**.

After revealing that γ,δ-epoxy-α,β-unsaturated esters are perfectly amenable reagents toward allylic arylation, we then extended our studies to their amide derivatives (**8**). Gladly, the use of a relatively smaller amount of **2** (1.5 equiv.) was sufficient for effective conversion of **8**, generally yielding the desired products in good to high yields (Table 3). The method operates well with both electron-rich and poor reagents **2** (entries 1–3). Although the structure of the amide group does not seem too critical for the process (entries 4–6), **9ca** could be isolated at a somewhat lower corresponding yield from the reaction of **8c**, containing relatively bulkier diisopropyl amide group (entry 5). Having larger groups on the oxirane terminus, such as propyl (**8e**) or cyclohexyl (**8f**), had no influence on the behaviour of the amide substrate (entries 7 and 8). It should be noted that an inferior result was obtained with its ester counterpart **1f** (Table 2, entry 8).

Conclusions

In conclusion, the palladium-catalysed reaction of γ,δ-epoxy-α,β-unsaturated esters or amides with $NaBAr_4$ reagents proceeded regio- and stereoselectively, specifically in *anti*-mode to produce allylic aryl-substituted homoallyl alcohols. While phosphine ligands showed very poor performance in terms of producing the desired product, $AsPh_3$ was found to be more suitable for the method, most likely because it increased the activity of the palladium at transmetalation step.

Experimental

General procedure for catalytic reactions

The reactions at <70 °C were carried out in a two-necked Schlenk attached to a condenser and inert gas-line, while those at ≥70 °C were performed in a sealed Schlenk tube under an inert gas.

The Pd-catalyst, ligand, and dry solvent (half of the volume required for reaction) were added, successively, into the Schlenk (dried in an oven and cooled under Ar gas) connected to an inert gas-line. The mixture was stirred for 5 min at rt, and then, organoboron, epoxide compound in a dry solvent (another quarter volume required for the reaction), additive, and base (in remaining last quarter volume of the dry solvent) were added successively. The mixture was stirred magnetically in a preheated oil bath. The reaction period was monitored by TLC when carried out in a two-necked Schlenk, while completion of the reaction was judged by the formation of palladium black when a sealed Schlenk tube was used. After completion of the reaction, the mixture was filtered through a short column of silica gel (height: 10 cm and width: 2 cm), washed with Et_2O, and concentrated under reduced pressure. The crude product was analysed by ^1H NMR using benzaldehyde as the internal standard. The residue was purified using silica gel column chromatography to afford the target product, the homoallylic alcohol **3** or **9** usually as a colourless oil.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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