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# Halide ion effects in the rhodium-catalyzed allylic substitution reaction using copper(I) alkoxides and enolates

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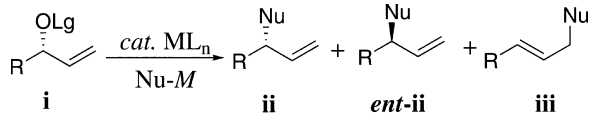
**Abstract**—The transmetallation of lithium alkoxides and enolates with a copper(I) halide salt provides the requisite nucleophiles to accomplish the stereospecific rhodium-catalyzed allylic substitution. These studies demonstrate that the nature of the halide ion derived from the copper(I) salt has a profound effect on regioselectivity and enantiospecificity. This observation was attributed to the *trans*-effect, by virtue of an in situ modification of the catalyst by the halide ion, which leads to *modulated* catalytic activity and improved stereospecificity.


## 1. Introduction

The transition metal-catalyzed allylic substitution is an important method for carbon–carbon and carbon–heteroatom bond construction, since it allows the introduction of a wide range of nucleophiles into an allylic framework (Eq. (1)).[1] Stabilized nucleophiles are typically employed in this type of reaction, due to the soft nature of the transition metal–allyl electrophile, whereas unstabilized nucleophiles are less common since they react through an alternative mechanism involving direct nucleophilic attack at the metal center. Nonetheless, the major limitation with this process has been the necessity to utilize allylic substrates that generate symmetrical metal–allyl intermediates in order to circumvent regiochemical infidelity. An equally important and challenging aspect of this transformation is the ability to control the absolute configuration of the newly formed stereogenic center.




(1)

The stereospecific rhodium-catalyzed allylic substitution provides a novel approach to this problem, in which unique and useful specificity can be obtained due to the propensity for the substitution to occur through a configurationally stable *distorted* π-allyl or *enyl* (σ+π) organorhodium intermediate.[2–5] The alkali metal salts of stabilized carbon, nitrogen, and oxygen nucleophiles provide efficient cross-coupling partners in the rhodium-catalyzed allylic substitution using malonates,[2] tosylamides,[3] and phenols.[4] Conversely, unstabilized nucleophiles, as exemplified by alkali metal alkoxides[6] and enolates,[7] were unsatisfactory due to competing side reactions and poor selectivity. We anticipated that the reactivity of alkoxide and enolate nucleophiles could be modulated through transmetallation with a copper(I) halide salt, and thereby soften the nucleophile. Indeed, copper(I) alkoxides[8] and enolates[9] provide optimum nucleophiles for the rhodium-allyl electrophile, as judged by the excellent specificity.[10,11] Herein, we describe a surprising halide effect on regioselectivity and enantiospecificity in the context of these reactions.[12] We also demonstrate that the allylic alkylation with copper enolates can be achieved using significantly reduced catalyst loading (0.5 mol%) with excellent regioselectivity and enantiospecificity, without dramatically compromising yield and specificity, making this a potentially useful transformation for process scale synthesis.

## 2. Results and discussion

Preliminary studies demonstrated that alkali metal alkoxides were not suitable nucleophiles for the rhodium-catalyzed allylic etherification reaction due to

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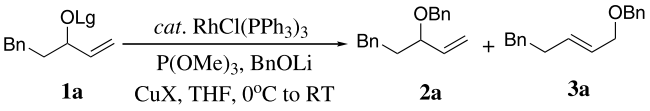
extensive side reactions (Table 1, entry 1). However, the transmetallation of the lithium alkoxide with copper(I) cyanide led to an efficient etherification, albeit with no discernable selectivity (entry 2). The utilization of a copper(I) halide salt led to a significant improvement in selectivity, in which there was a pronounced halide effect (I > Br > Cl) on regioselectivity (entries 3–5).[13] Additional improvements in the efficiency of the transformation were realized by increasing the steric bulk of the leaving group to suppress competitive transacylation (entry 6).

This halide ion effect is most easily explained through an in situ salt metathesis reaction between the rhodium–chloride catalyst and the resulting lithium cyanide or halide salts.[14] Thus, the rhodium–iodide catalyst appears to be the most effective in terms of affording the branched product selectively, while the rhodium–cyanide catalyst shows no preference for either regioisomer. Additional studies demonstrated the rhodium-catalyzed allylic etherification is compatible with primary, secondary, and tertiary copper alkoxides using an array of substituted secondary allylic carbonates.[10]

**Table 1.** Effect of copper(I) salts on the regioselective rhodium-catalyzed allylic etherification




**1a** **2a** **3a**

| Entry | Leaving group Lg[a] | X | 2°:1° **2a**:**3a**[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | $CO_2Me$ | – | 9:1 | 4 |
| 2 | $CO_2Me$ | CN | 1:1 | 73 |
| 3 | $CO_2Me$ | Cl | 44:1 | 58 |
| 4 | $CO_2Me$ | Br | 72:1 | 66 |
| 5 | $CO_2Me$ | I | ≥99:1 | 73 |
| ***6*** | ***$CO_2{}^tBu$*** | ***I*** | ***≥99:1*** | ***96*** |

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol% of $RhCl(PPh_3)_3$ *modified* with 40 mol% $P(OMe)_3$, 1.9 equiv. of the lithium alkoxide, and 2.0 equiv. of CuX.

[b] Ratios of regioisomers were determined by capillary GLC on aliquots of the crude reaction mixture.

[c] GLC yields.

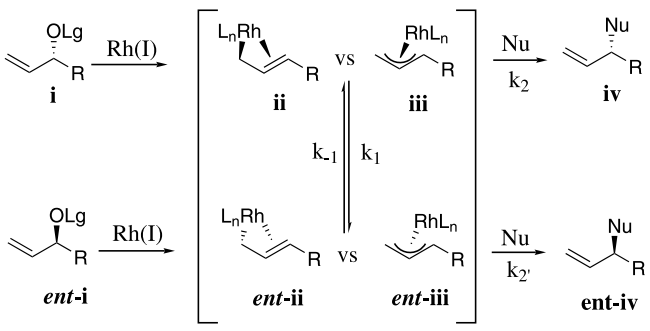



**Figure 1.**

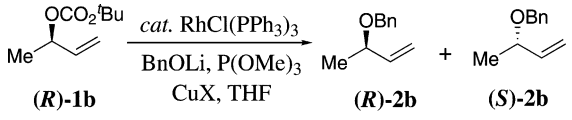
Encouraged by the excellent regioselectivity, we turned our attention to stereospecificity. A general assessment of the metal-catalyzed allylic alkylation indicates that the reaction could proceed through either a configurationally stable *enyl* **ii** or a distorted π-allyl **iii** organometallic species, as depicted in Figure 1. We had originally envisioned that the stereospecificity could be maintained by suppressing the rate of isomerization of the initial *enyl* or metal–allyl intermediate relative to $S_N2'$ substitution, by adjusting the electronic environment and/or coordination sphere of the metal. Although the dynamics of this isomerization are complex, the ability to control the rate of isomerization provided the key to the stereospecific metal-catalyzed allylic substitution reaction. Hence, in order for the etherification reaction to be stereospecific, nucleophilic trapping by the copper(I) alkoxide must be faster than racemization of the rhodium–allyl intermediate (i.e. for **i** $k_2 \gg k_1$ and for ***ent*-i** $k_{2'} \gg k_{-1}$) through a (π-σ-π) isomerization mechanism (Fig. 1).

The examination of the stereospecificity of the etherification provided the most dramatic halide effect, as outlined in Table 2. Treatment of enantiomerically enriched allylic carbonate **(*R*)-1b** (94% ee) under optimized conditions, furnished the allyl ether **(*R*)-2b** in 84% yield (2°:1° ≥ 99:1), albeit with poor enantiospecificity (41% cee; entry 1). This result represented a significant departure from our earlier studies and thus prompted the examination of the other copper(I) halide salts. Interestingly, the transmetallation with copper(I) chloride or bromide, furnished the allylic ether **(*R*)-2b** with significantly improved chirality transfer (entries 2–3). Moreover, the trend for enantiospecificity is opposite that for regioselectivity, indicating that they are independent of one another. Additional work demonstrated that the optimal stereospecificity was obtained at lower temperature (entry 4).

While it is difficult to completely discount the role of the halide on the metal center's ability to influence the rate of nucleophilic trapping, this cannot be excluded as a possibility. However, a more likely scenario involves the halide's ability to influence the rate of π-σ-π isomerization. This phenomenon is supported by the fact that the amount of racemization caused by the various rhodium–halide catalysts parallels the strength of the *trans*-effect[15,16] attributed to each halide ligand (I > Br > Cl). Thus if the π-component of the *enyl* ligand is *trans* to the halide in the rhodium–allyl intermediate, then dissociation of the π-component of the enyl intermediate, leading to a σ-allyl will be most facile when the halide ligand is iodide. Although speculative, this *trans*-effect adequately explains the observed trend in enantiospecificity for the etherification reaction.

In light of the halide effects, we decided to probe the role of the copper alkoxide and the lithium halide, derived from the transmetallation, by preparing the copper alkoxide under salt free conditions, as outlined in Table 3. Mesityl copper was chosen to provide the copper(I) alkoxide because the metal halide salts are removed during its preparation. Interestingly, only a

**Table 2.** Influence of the copper(I) halide salt on enantiospecificity

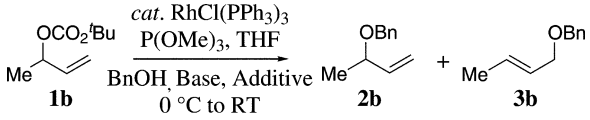



(*R*)-1b (*R*)-2b (*S*)-2b

| Entry | Copper halide salt[a] | Temp. | 2°:1° **2b**:**3b**[b] | cee (%)[c] | Yield (%)[d] |
|---|---|---|---|---|---|
| 1 | CuI | 0°C–RT | ≥99:1 | 41 | 84 |
| 2 | CuBr | 0°C–RT | 91:1 | 85 | 86 |
| 3 | CuCl | 0°C–RT | ≥99:1 | 88 | 81 |
| ***4*** | ***CuCl*** | ***−10°C*** | ***≥99:1*** | ***96*** | ***81*** |

[a] All reactions were carried out on a 0.5 mmol reaction scale.
[b] Ratios of regioisomers were determined by capillary GLC on the crude reaction mixture.
[c] Enantiomeric excess was determined by chiral capillary GLC.
[d] GLC yields.

**Table 3.** Probing the role of lithium iodide and the copper(I) alkoxide in the allylic etherification




1b 2b 3b

| Entry | Base[a] | Additive | 2°:1° **2b**:**3b**[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | LiHMDS | CuI | ≥99:1 | 84 |
| 2 | Mesityl copper | – | 7:1 | 3 |
| 3 | LiHMDS | LiI | 86:1 | 4 |
| 4 | Mesityl copper | LiI | ≥99:1 | 76 |

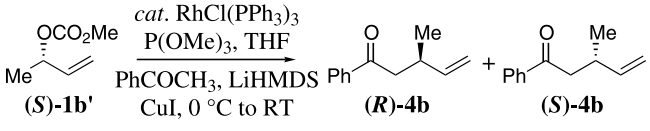
[a] All reactions were carried out on a 0.5 mmol reaction scale.
[b] Ratios of regioisomers were determined by capillary GLC on the crude reaction mixture.
[c] GLC yields.

trace of product was observed in the absence of lithium iodide (entry 2). Conversely, the addition of lithium iodide to the lithium alkoxide also furnished a trace amount of the allylic ether **2b**, indicating the necessity for copper (entry 3). When lithium iodide is added to the copper alkoxide derived from the alcohol and mesityl copper, analogous turnover and regioselectivity are obtained (entry 4 vs 1). This clearly indicates that the copper alkoxide and lithium iodide are both required for optimal catalytic activity.

Although the exact role of lithium iodide remains unclear, it may function to reconstitute a catalytically inactive rhodium–alkoxide complex into a catalytically active rhodium–halide complex. The addition of lithium iodide to the reaction with a lithium alkoxide is catalytically inferior, proving that the copper is vital to the reaction. It appears that the copper(I) alkoxide is crucial for nucleophilic trapping of the soft rhodium–allyl electrophile, while lithium iodide, derived from the transmetalation, may be involved in regenerating the active catalyst.

The concept of modulating the reactivity of a nucleophile through the transmetalation with a copper(I) halide was extended to enolates with the notion that this would soften its basic character. We anticipated that the copper(I) enolate would circumvent problems associated with the corresponding lithium enolate, namely polyalkylation, poor regio- and stereocontrol and poor chemical yield. Preliminary optimization demonstrated that although the transmetalation is crucial for efficient conversion and selectivity, the nature of the copper(I) halide salt was inconsequential to the stereospecificity (I ~ Br ~ Cl), in sharp contrast to the previous studies with copper alkoxides. This is due presumably to the favorable matching of the nucleophilicity the copper(I) enolate with the rhodium-allyl intermediate, which results in direct alkylation prior to equilibration via π-σ-π isomerization.

Treatment of the enantiomerically enriched secondary allylic carbonate **(*S*)-1b′** with the lithium enolate of acetophenone, transmetallated with copper(I) iodide, using 10 mol% of the trimethylphosphite-modified Wilkinson's catalyst at 0°C, furnished the alkylation product **(*R*)-4b** in 91% yield with excellent regioselectivity and enantiospecificity (2°:1° ≥ 99:1, cee = 100%, Eq. (2)). In light of the immense synthetic utility of this transformation, additional studies focused on reducing the catalyst loading to make the reaction more cost effective. Interestingly, the amount of catalyst was readily reduced without significantly compromising selectivity, and with similar efficiency, albeit with slightly more dialkylation (13%).[17] *Hence, the rhodium-catalyzed allylic alkylation of* ***(S)-1b′*** *with the copper enolate of acetophenone was performed on a 100 mmol scale with only 0.5 mol% catalyst, to afford the ketone* ***(R)-4b*** *in 70% yield with excellent selectivity (2°:1° ≥ 99:1, cee = 95%).*

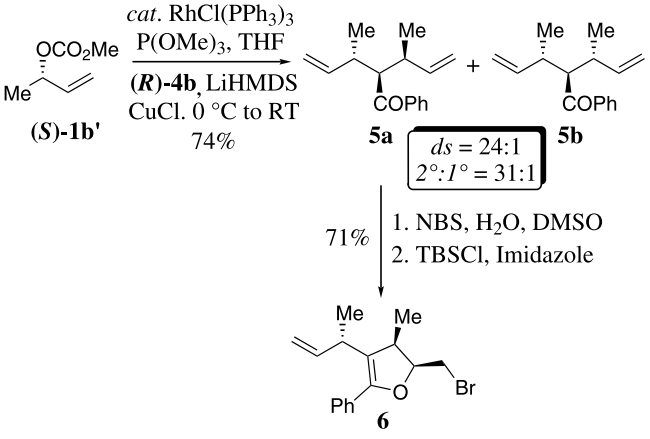



(*S*)-1b' (*R*)-4b (*S*)-4b

(2)

The stereocontrolled construction of 1,3-carbon stereogenic centers, including pseudo $C_2$-symmetrical fragments, represent an important process for organic synthesis.[18] We envisioned that acetophenone could serve as a linchpin, allowing two sequential allylic alkylations to provide the ketone **5a**, which upon desymmetrization could afford the potentially useful synthon **6** in an expeditious manner (Scheme 1). The second allylic alkylation, using the copper iodide derived enantiomerically enriched enolate **(*R*)-4b** and the allylic carbonate **(*S*)-1b′** (97% ee) proved a considerably more challenging alkylation than expected, providing **5a**/**b** in 77% yield, albeit with modest diastereo-

selectivity favoring **5a** (ds = 5:1, 2°:1° = 34:1). Since the reaction is otherwise identical to the previous alkylation (Eq. (2)), the poor diastereocontrol is presumably the result of equilibration of the rhodium–allyl intermediate, which is due in part to a slower alkylation with the more sterically hindered enolate of **(*R*)-4b**. We anticipated that the poor diastereoselectivity could be circumvented using a different copper(I) halide salt, with the expectation that the rhodium–allyl intermediate would be less prone to equilibration. Treatment of the allylic carbonate **(*S*)-1b′** with the copper enolate of **(*R*)-4b** derived from the transmetallation with copper chloride, furnished **5a** in 74% yield, and with excellent diastereoselectivity (ds = 24:1, 2°:1° = 37:1). The improved diastereoselectivity is consistent with the trend observed using copper(I) alkoxides, wherein the chloride ion show enhanced stereospecificity as compared to their iodide derived counterparts.




**Scheme 1.**

This study confirms that the iodide anion either promotes more rapid equilibration of the rhodium–allyl intermediate or less rapid nucleophilic trapping of that intermediate compared to the chloride ion. This may be attributed to the in situ generation of an iodo-rhodium catalyst from the chloro-rhodium species. Nevertheless, the iodide anion seems to cause racemization in more demanding cases where nucleophilic trapping is presumably slower. The *pseudo* $C_2$-symmetrical linchpin alkylation product **5a** was then desymmetrized using a novel bromoetherification reaction, where the addition of water to the ketone allows for a selective bromoetherification followed by elimination of the in situ silyl protected hemiketal, to furnish **6** in 71% yield with excellent diastereoselectivity (ds ≥ 19:1 by NMR).[19] The stereochemical assignment was made with the aid of an NOE experiment.

## 3. Conclusion

In conclusion, we have demonstrated the transmetallation of lithium alkoxides and enolates with copper halide salts provide the requisite nucleophiles to facilitate the stereospecific rhodium-catalyzed allylic substitution. This study also demonstrated that the nature of the halide ion derived from the copper(I) salt has a profound effect on regioselectivity and enantiospecificity. This observation was attributed to the *trans*-effect, by virtue of an in situ modification of the catalyst by the halide ion, leading to *modulated* catalytic activity and ultimately improved stereospecificity. We also demonstrated that the catalyst loading could be significantly reduced upon scale-up, for the enolate alkylation, making it a more attractive method for process development. Overall, this work provides yet another example of the important role that halides play in metal-catalyzed reactions.

## 4. Experimental

### 4.1. General

All reactions were carried out in flame-dried glassware, and under an atmosphere of argon or nitrogen. Tetrahydrofuran (THF) was continuously distilled from sodium benzophenone ketyl, *N*,*N*-dimethylformamide (DMF) was distilled from $CaH_2$, dimethylsulfoxide (DMSO) was used without purification or drying. Trimethyl phosphite was distilled from $CaH_2$ and stored over 4 Å molecular sieves. Benzyl alcohol was distilled from $MgSO_4$ and stored over 3 Å molecular sieves. Acetophenone was distilled from $MgSO_4$. All copper salts were dried in a vacuum at 160°C for 12 h and stored in the dark. Lithium iodide was dried in a vacuum at 160°C for 12 h and stored and handled in a glove box. Mesityl copper was prepared using literature procedures, stored, and handled in a glove box.[20] *N*-Bromosuccinimide was recrystallized from water and dried in a vacuum desiccator over $P_2O_5$. All allylic carbonates were prepared using literature procedures and distilled before use. All other reagents were purchased from Acros, Aldrich, Fluka, or Lancaster chemical companies and were used without purification unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck 60 $F_{254}$ precoated silica gel plates. Flash chromatography was conducted using Merck Silica Gel 60 (230–400 mesh).

### 4.2. (*R*)-3-Methyl-1-phenylpent-4-en-1-one (*R*)-4b

Trimethyl phosphite (240 μL, 2.0 mmol) was added directly to a red suspension of Wilkinson's catalyst (464.6 mg, 0.50 mmol) in anhydrous THF (20 mL) and then stirred under an atmosphere of argon. The catalyst was allowed to form over ca. 15 min resulting in a light yellow homogeneous solution. Lithium hexamethyldisilyl azide (190 mL, 190 mmol, 1.0 M solution in THF) was added dropwise over a period of 5 min to a suspension of copper(I) iodide (38.107 g, 200 mmol, previously dried in vacuo at 160°C) and acetophenone (23.3 mL, 200 mmol) in anhydrous THF (500 mL) under an atmosphere of argon. The enolate was allowed to form over ca. 5 min until a brown homogeneous solution was obtained. The catalyst and the enolate solutions were then cooled with stirring to 0°C, and the former added via Teflon cannula to the copper

enolate solution, followed by the addition of the allylic carbonate **(*S*)-1b** (13.037 g, 100 mmol, ee = 97%) in anhydrous THF (80.0 mL) via Teflon cannula. The reaction was allowed to slowly warm to room temperature over ca. 16 h resulting in a brown heterogeneous solution (TLC control). The reaction mixture was quenched with $NH_4Cl$ solution (500 mL) and partitioned between diethyl ether and saturated aqueous $NH_4Cl$ solution. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 1% ethyl acetate/hexanes) furnished the ketone **(*R*)-4b** (12.250 g, 70%) as a colorless oil: $[\alpha]_D^{24}$ +1.3 (*c* 1.35, $CHCl_3$); chiral HPLC analysis (Diacel® AD-H column) ee = 92%, Racemic GC analysis (HP-1 methyl siloxane capillary column) 2°:1° ≥ 99:1; IR (neat) 3082 (w), 2963 (m), 2929 (w), 2857 (w), 1686 (s), 1641 (w), 1598 (m), 1449 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.94–7.92 (m, 2H), 7.54 (t, $J$ = 7.4 Hz, 1H), 7.44 (t, $J$ = 7.6 Hz, 2H), 5.83 (ddd, $J$ = 17.0, 10.5, 6.5 Hz, 1H), 5.01 (dt, $J$ = 17.3, 1.2 Hz, 1H), 4.94 (d, $J$ = 10.5 Hz, 1H), 3.01 (dd, A of ABX, $J_{AB}$ = 18.2 Hz, $J_{AX}$ = 9.0 Hz, 1H), 2.92–2.85 (m, 1H), 2.88 (dd, B of ABX, $J_{AB}$ = 18.0 Hz, $J_{BX}$ = 6.9 Hz, 1H), 1.08 (d, $J$ = 6.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.59 (e), 143.27 (o), 137.51 (e), 133.18 (o), 128.79 (o), 128.32 (o), 113.26 (e), 45.36 (e), 33.82 (o), 20.02 (o); HRMS (CI, $M^+$) calcd for $C_{12}H_{14}O$ 174.1045, found 174.1048.

### 4.3. (3*S*,1′*S*)-3-Methyl-2-(1-methylprop-2-en-1-yl)-1-phenylpent-4-en-1-one 5a

Trimethyl phosphite (24 μL, 0.20 mmol) was added directly to a red suspension of Wilkinson's catalyst (46.5 mg, 0.05 mmol) in anhydrous THF (2.0 mL) and then stirred under an atmosphere of argon. The catalyst was allowed to form over ca. 15 min resulting in a light yellow homogeneous solution. Lithium hexamethyldisilyl azide (950 μL, 0.95 mmol, 1.0 M solution in THF) was added dropwise to a suspension of copper(I) chloride (89.2 mg, 1.00 mmol, previously dried in vacuo at 160°C) and **(*R*)-4b** (178.8 mg, 1.03 mmol, ee = 97%,) in anhydrous THF (3.0 mL) under an atmosphere of argon and the anion was allowed to form over ca. 2 min until a light yellow/green homogeneous solution was obtained. The catalyst and the enolate solutions were then cooled with stirring to 0°C, and the former added via Teflon cannula to the copper enolate solution. The allylic carbonate **(*S*)-1b** (64.9 mg, 0.50 mmol, ee = 97%) was then added via a tared 500 μL gastight syringe to the catalyst/enolate mixture, and the reaction was allowed to slowly warm to room temperature over ca. 4 h (TLC control) resulting in a tan heterogeneous solution. The reaction mixture was quenched with $NH_4Cl$ solution (1 mL) and partitioned between diethyl ether and saturated aqueous $NH_4Cl$ solution. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 1% ethyl acetate/hexanes) furnished the ketone **5a** (84.3 mg, 74%) as a colorless oil: $[\alpha]_D^{25}$ +38.8 (*c* 1.16, $CHCl_3$); racemic GC analysis (HP-1 methyl siloxane capillary column) 2°:1° = 37:1, ds = 24:1; IR (neat) 3076 (w), 2969 (m), 2931 (m), 2871 (w), 1678 (s), 1640 (m), 1596 (m), 1580 (m), 1450 (m), 1420 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (dt, $J$ = 7.1, 1.7 Hz, 2H), 7.53 (tt, $J$ = 7.4, 1.5 Hz, 1H), 7.43 (t, $J$ = 7.6 Hz, 2H), 5.89–5.80 (m, 1H), 5.68 (ddd, $J$ = 17.2, 10.2, 8.6 Hz, 1H), 5.08–4.92 (m, 4H), 3.41 (dd, $J$ = 8.8, 5.9 Hz, 1H), 2.78–2.64 (m, 2H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H; $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 203.74 (e), 142.39 (o), 140.72 (o), 139.96 (e), 132.96 (o), 128.76 (o), 128.44 (o), 115.03 (e), 114.81 (e), 55.40 (o), 39.19 (o), 38.94 (o), 19.15 (o), 18.26 (o); HRMS (CI, $M^+$) calcd for $C_{16}H_{20}O$ 228.1514, found 228.1510.

### 4.4. (2*S*,3*R*,1′*S*)-2-(Bromomethyl)-3-methyl-4-(1-methylprop-2-en-1-yl)-5-phenyl-2,3-dihydrofuran 6

*N*-Bromosuccinimide (16.7 mg, 0.09 mmol) was added in one portion to a solution of **5** (20.8 mg, 0.09 mmol) in DMSO (0.5 mL) and water (1.6 μL, 0.09 mmol) then stirred under an atmosphere of nitrogen for ca. 1 h (TLC control). The reaction was then partitioned between diethyl ether and water. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 10% ethyl acetate/hexanes) furnished the epimeric hemiketals (25.1 mg, 85%) as a colorless oil. *tert*-Butyldimethylsilyl chloride (33.2 mg, 0.22 mmol) was added in one portion to a solution of the epimeric hemiketals (31.5 mg, 0.10 mmol) and imidazole (19.2 mg, 0.28 mmol) in DMF (0.5 mL) then stirred under an atmosphere of nitrogen for 72 h (TLC control). The reaction was partitioned between diethyl ether and water. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 10% dichloromethane/hexanes) furnished **6** (25.0 mg, 84%) as a colorless oil. $[\alpha]_D^{25}$ −43.0 (*c* 1.01, $CHCl_3$); IR (neat) 3082 (w), 2968 (s), 2929 (m), 2876 (m), 1636 (m), 1602 (m), 1494 (m), 1446 (m) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (dd, $J$ = 7.0, 1.5 Hz, 2H), 7.35 (t, $J$ = 7.4 Hz, 2H), 7.29 (tt, $J$ = 7.3, 2.8 Hz, 1H), 5.89 (ddd, $J$ = 17.2, 10.4, 5.6 Hz, 1H), 5.03 (dt, $J$ = 17.2, 1.5 Hz, 1H), 5.01 (dt, $J$ = 10.3, 1.4 Hz, 1H), 4.65 (q, $J$ = 7.4 Hz, 1H), 3.65 (dd, A of ABX, $J_{AB}$ = 10.2 Hz, $J_{AX}$ = 6.4 Hz, 1H), 3.55 (dd, B of ABX, $J_{AB}$ = 10.2 Hz, $J_{BX}$ = 7.9 Hz, 1H), 3.47 (pentet, $J$ = 7.1 Hz, 1H), 3.01 (pentet, $J$ = 7.2 Hz, 1H), 1.30 (d, $J$ = 7.1 Hz, 3H), 1.12 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.20 (e), 141.98 (o), 131.66 (e), 128.55 (o), 128.42 (o), 127.86 (o), 119.94 (e), 113.57 (e), 82.85 (o), 40.86 (o), 34.75 (o), 29.74 (e), 19.97 (o), 13.92 (o); HRMS (CI, $M^+$) calcd for $C_{16}H_{19}BrO$ 306.0619, found 306.0611.

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