# Asymmetric Synthesis of Homoallylic Alcohols featuring Vicinal Tetrasubstituted Carbon Centers via Dual Pd/Photoredox Catalysis

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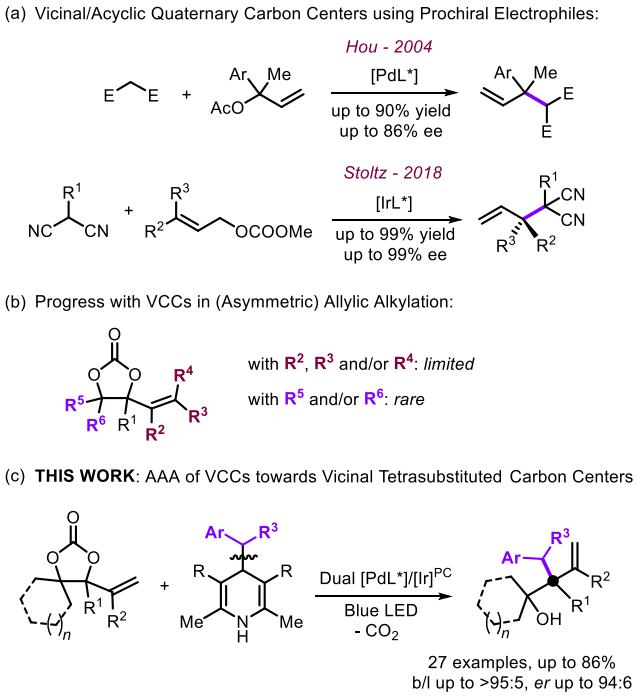
**Abstract:** Dual palladium/photoredox-catalysis provides an effective method for the asymmetric synthesis of vicinal α,β-tri/tetra- or α,β-tetra-substituted homoallylic alcohols. Regio- and enantioselective decarboxylative allylic alkylation of vinyl cyclic carbonates is reported using Hantzsch type esters as radical precursors. The developed methodology combines the use of versatile and accessible reagents and can be operated under mild reaction conditions giving the target molecules in appreciable to good yields, high branch-selectivity and appreciable enantiomeric ratios of up to 94:6. This protocol marks a rare example of the use of prochiral electrophiles for the creation of vicinal congested carbon centers

**Introduction:** Chiral quaternary carbon centers are ubiquitous in natural products and pharmaceuticals,[1] but still present chemical challenges in their synthesis. While significant progress has been made over the recent decades in the asymmetric construction of quaternary carbon stereocenters,[2] the enantioselective formation of acyclic vicinal tetrasubstituted carbon centers represents a more daunting challenge.[1a+b,3] Among the strategies that have proven to be both versatile and effective, asymmetric allylic alkylation (AAA) represents one of the most powerful methods for the construction of carbon-carbon bonds resulting in quaternary carbon stereocenters.[2a-b,g,4] Two main AAA approaches are known that exploit stereocontrol over either prochiral nucleophiles[5] or prochiral electrophiles.[6] Although various efficient metal-assisted protocols have been established, to date the enantioselective preparation of organic target molecules comprising acyclic vicinal tetrasubstituted carbon centers utilizing prochiral electrophiles remains underexplored (Scheme 1a).

Pd-catalyzed asymmetric allylic substitution reactions of vinyl epoxides[7] and vinyl cyclic carbonates (VCCs)[8] serving as prochiral electrophilic allylic surrogates have been recently reported as efficient approaches to forge compounds featuring a tetrasubstituted carbon stereocenter. While only a handful of studies report the efficient use of olefin-substituted VCCs in allylic alkylation (Scheme 1b, $R^2$-$R^4 \neq H$)[9] and more particularly towards branched allylic products,[9h,i] as far as we are aware only two reports exist that briefly discuss the use of more elaborate carbonate ring substituted congeners (Scheme 1b, $R^5$ and $R^6 \neq H$).[9f,g] The successful conversion of these latter types of congested substrates in transformations leading to compounds having vicinal tetrasubstituted carbon

centers would greatly expand the application potential of VCCs and advance the synthesis of otherwise elusive carbon stereocenters.




**Scheme 1. (a) Limited Progress with Prochiral Electrophiles, (b) Limitations in the use of VCCs (b) and (c) Current Approach towards Elusive Stereocenters using AAA Strategies.**

In order to expedite the potential of these challenging functional substrates in allylic alkylation processes, we envisioned that the use of dual transition metal/photoredox catalysis[10] could offer an alternative yet powerful approach that could circumvent the limitations encountered in classical catalytic allylic substitution reactions (cf., Scheme 1b). Herein, we report the combination of photoredox and Pd-catalyzed AAA of vinyl cyclic carbonates using Hantzsch type esters as radical precursors[11] affording homoallylic alcohol products with either α,β-tri/tetra- or α,β-tetra-substituted carbon centers (Scheme 1c). The developed protocol combines mild reaction conditions, avoids the use of stoichiometric organometallic reagents and produces a series of products with acyclic vicinal tetrasubstituted carbon centers in good yields and high regio- and enantiocontrol.

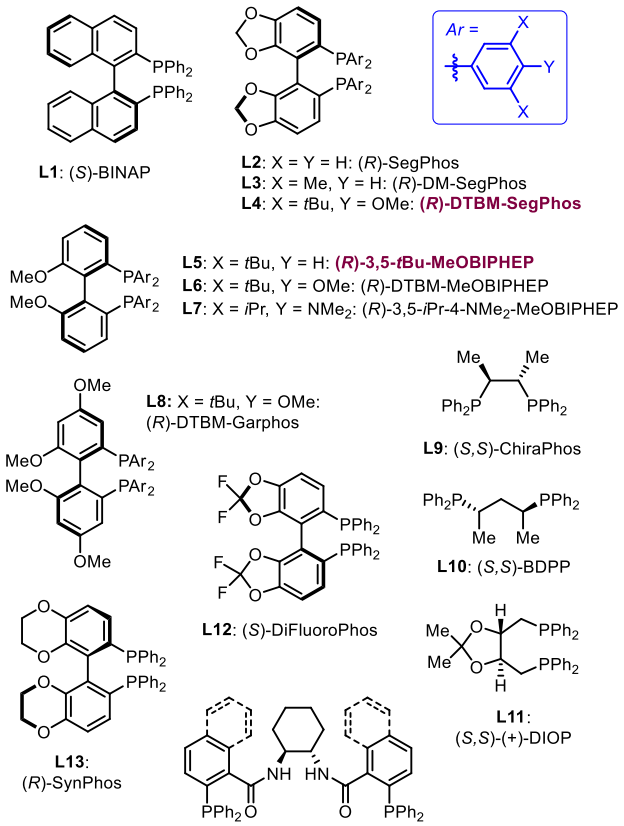
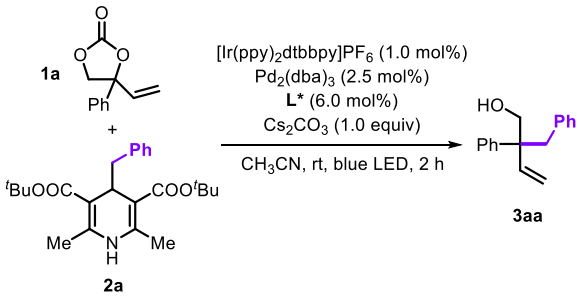



**Figure 1**. Phosphine-based ligands of Table 1.

**Results and discussion:** We started our investigation by using VCC **1a** and substituted Hantzsch ester **2a** and examining the envisioned coupling while screening a variety of chiral ligands, Ir-based photocatalysts, solvents and base additives (Supporting Information, SI: Tables S1-S5). The most relevant selection of these data is provided in Table 1. After determining the most effective photocatalyst (PC, $Ir(ppy)_2(dtbbpy)PF_6$), type of base ($Cs_2CO_3$) and solvent (acetonitrile), a wide variety of chiral diphosphine ligands (see Figure 1 and SI) were scrutinized in the benchmark protocol.

The use of BINAP as a chiral ligand (entry 1) did not lead to any asymmetric induction and **3aa** was produced in a low yield (25%). The utilization of Segphos type diphosphines proved to be more productive (entries 2-4), and variation of the P-aryl groups gave **3aa** in 60% yield with excellent regio- (b:l >95:5) and appreciable enantio-selectivity (*er* = 86:14). Structurally related BIPHEP and Garphos ligands (entries 4-8) also provided good results, with the use of **L5** being most efficient (entry 5: 71%, b:l >95:5, *er* = 89:11).

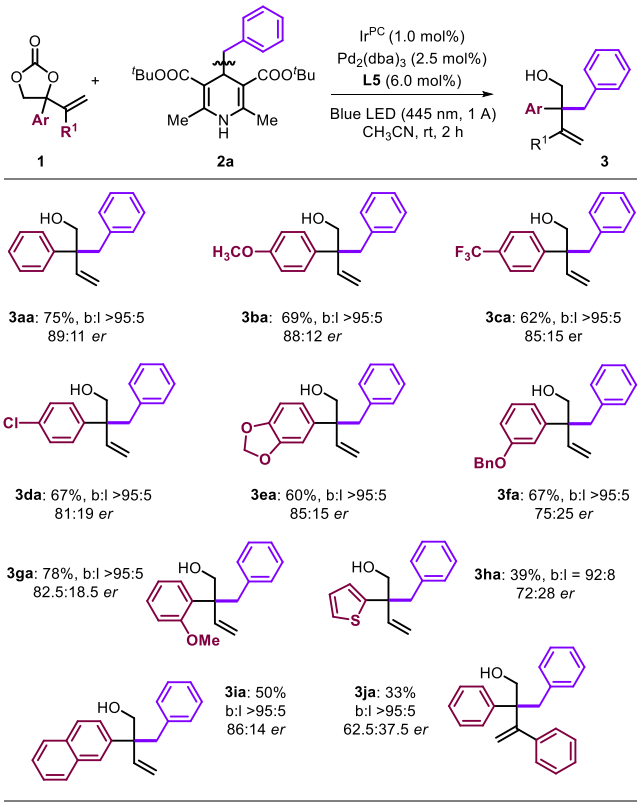
**Table 1.** Part of the Screening Data towards the Synthesis of Homoallylic Alcohol 3aa.[a]




| entry | L* | yield (%)[a] | b/l[a] | *er*[a] |
|---|---|---|---|---|
| **1** | **L1** | 25 | 65:35 | 0 |
| **2** | **L2** | 26 | 64:36 | 64:36 |
| **3** | **L3** | 31 | 70:30 | 63:37 |
| **4** | **L4** | 60 | >95:5 | 86:14 |
| **5** | **L5** | 71 | >95:5 | 89:11 |
| **6** | **L6** | 66 | >95:5 | 84:16 |
| **7** | **L7** | 65 | >95:5 | 86:14 |
| **8** | **L8** | 60 | 93:7 | 85:15 |
| **9** | **L9** | 12 | 22:78 | - |
| **10** | **L10** | 16 | 31:69 | 50.5:40.5 |
| **11** | **L11** | 12 | 28:72 | - |
| **12** | **L12** | 28 | 73:26 | 40:60 |
| **13** | **L13** | 30 | 61:39 | 63:37 |
| **14** | **L14** | 11 | 27:73 | - |
| **15** | **L15** | 12 | 22:78 | - |
| **16**[b] | **L4** | 65 | >95:5 | 87.5:12.5 |
| **17**[c] | **L4** | 25 | 61:39 | 87.5:12.5 |
| **18**[d] | **L4** | 0 | - | - |
| **19**[e] | **L4** | 71 | >95:5 | 88:12 |
| **20**[e] | **L5** | 75 | >95:5 | 89:11 |

[a]**1a** (0.10 mmol), **2a** (0.15 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1.0 mol%), $Pd_2(dba)_3$ (2.5 mol%), L* (6.0 mol%), $Cs_2CO_3$ (0.10 mmol) were combined in $CH_3CN$ (2.0 mL) at 25 °C under blue LED radiation (445 nm, 0.7 A, corresponding to a photon flux of 1.2 µeinstein/s) for 2 h. Yields and b/l ratios were determined by $^1H$ NMR analysis using $CH_2Br_2$ as an internal standard. Enantiomeric ratios (*er*) were determined by UPC2. [b]In the absence of $Cs_2CO_3$. [c]In the absence of $Ir(ppy)_2(dtbbpy)PF_6$. [d]In the dark. [e]In the absence of $Cs_2CO_3$, under blue LED radiation (445 nm, 1.0 A, corresponding to a photon flux of 1.6 µeinstein/s).

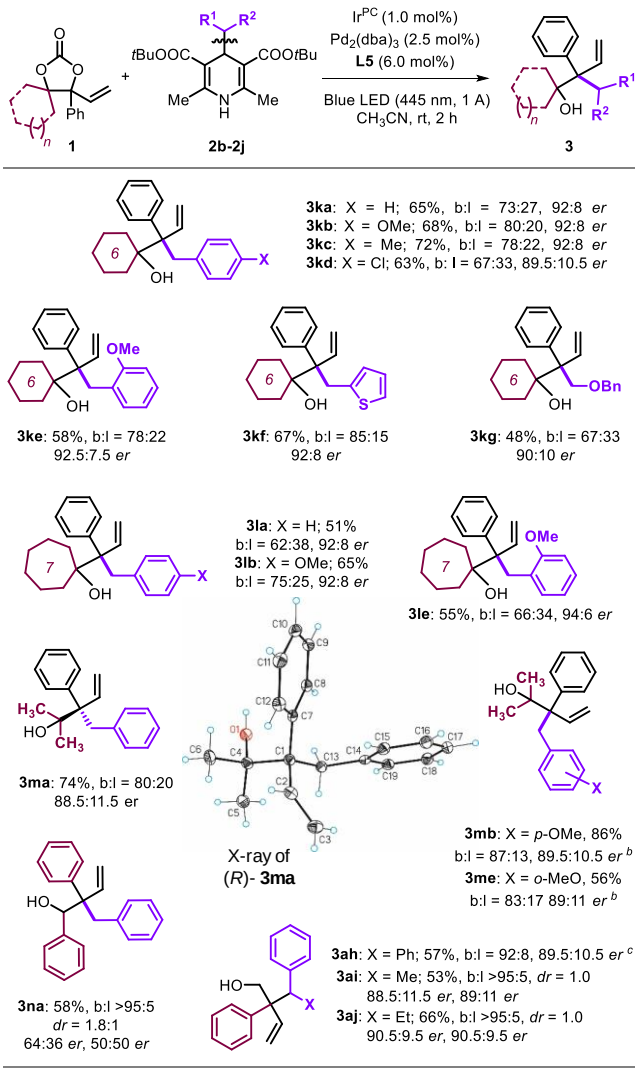
The use of other diphosphine ligands (**L9**-**L15**) did not improve the process outcome (entries 9-15). Further variations of the protocol (entries 16-19) were first carried out with (*R*)-DTBM-SegPhos being cheaper than (*R*)-3,5-*t*Bu-MeOBIPHEP, but providing nearly the same regio- and enantiocontrol (cf., entries 4 versus 5). In the absence of $Cs_2CO_3$, **3aa** was obtained in a slightly higher yield and *er* (entry 16 versus 4), and therefore was omitted for the optimized conditions (*vide infra*). Omitting the iridium PC (entry 17) gave **3aa** in 25% yield suggesting that Hantzsch ester **2a** could itself also serve as a photoreductant to form a radical cation that subsequently generates, through homolytic cleavage, the requisite alkyl radical for the C–C coupling.[12] As expected, no product was detected without blue LED irradiation, but by further increasing the light intensity, the yield of **3aa** increased to 71% (entry 19). With these alternative conditions in hand, we then re-used (*R*)-3,5-tBu-MeOBIPHEP **L5** as ligand, which afforded the product in 75% yield and with an *er* of 89:11 (entry 20).




**Scheme 2.** Product scope using various VCCs to generate quaternary carbon stereocenters. Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1.0 mol%), $Pd_2(dba)_3$ (2.5 mol%), (*R*)-3,5-*t*Bu-MeOBIPHEP **L5** (6.0 mol%), $CH_3CN$ (2 mL), 2 h, blue LED (445 nm, 1 A, corresponding to a photon flux of 1.6 µeinstein/s). Yields of the isolated, column-purified products are reported. The enantiomeric ratios (*er* values) were determined by UPC2. The b/l ratios were determined by $^1H$ NMR analysis.

With these optimized conditions we then examined the generality of similar substrate combinations providing homoallylic alcohols with quaternary carbon stereocenters (Scheme 2, **3aa**-**3ja**). Variation of the aryl substituents on the VCC in the presence of Hantzsch ester **2a** generally provided the homoallylic alcohols with remarkable branch-selectivity (b:l >95:5) and in appreciable isolated yields of up to 78% (**3ga**). Good enantio-induction levels of up to 89:11 *er* for the majority of the products were achieved except for **3fa**, **3ha** and **3ja**. Whereas for **3ha** the presence of the thiophen-2-yl group could interfere through coordination to Pd(allyl) intermediates, the use of a

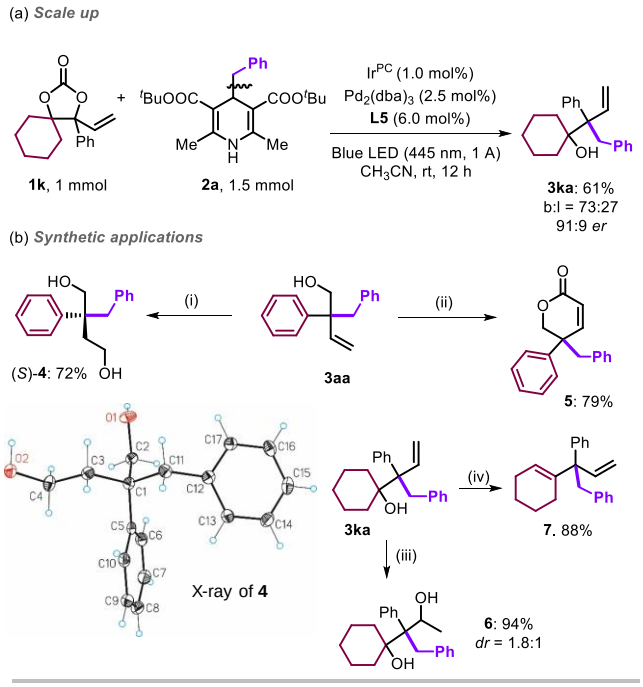
VCC with an additional substituent ($R^1$ = Ph, **1j**) on the vinyl group hence increasing the steric demand substrate activation was detrimental to both the product yield (33%) and optical purity (62.5:37.5 *er*).




**Scheme 3.** Product scope using various VCCs to generate chiral homoallylic alcohols having vicinal tetrasubstituted carbon centers. Reaction conditions are the same as in Scheme 2. Yields of the isolated, column-purified products are reported. The enantiomeric ratios (*er* values) were determined by UPC2. The b/l ratios were determined by $^1$H NMR analysis. [b]Reaction time was 4 h. [c]The corresponding Hantzsch nitrile was used.

In a second, more dedicated embodiment of the substrate scope we primarily selected VCCs with further substitution on the carbonate ring (Scheme 3). VCC **1k** (incorporating a spiro-fused cyclohexyl group) was first chosen and combined with several Hantzsch esters furnishing **3ka**-**3kg**. In these sterically frustrated transformations, the b:l ratios remained in most cases practical allowing to isolate the pure, branched homoallylic alcohols in moderate to good yields (48-72%). Furthermore, the conversion of **1k** proceeded smoothly with a quantum yield 6.8% leading to complete conversion within 20 min (see SI).[13] Despite the more complex nature of these couplings compared to the ones presented in Scheme 2, slightly higher enantiomeric ratios of up to 92.5:7.5 were noted. Increasing the size of the spiro-cycloalkyl group in the VCC (**3la**, **3lb** and **3ld**) was feasible and the protocol was effective towards the formation of chiral homoallylic alcohol products in reasonable yields and with

*er* values of up to 94:6. Next, an acyclic substitution on the tetrasubstituted VCC substrates was examined (i.e., **1m**) delivering the target products **3ma** and **3mb** with slightly higher b:l ratios and isolated yields (for **3ma**, 74%, and **3mb**, 86%).




**Scheme 4.** (a) Scale-up and (b) product diversification. Reaction conditions: (i) $BH_3$·THF, dry THF, 0 ºC, 3 h; then NaOH, $H_2O_2$. (ii) acryloyl chloride, DIPEA, $CH_2Cl_2$, rt, 2 h; then $H_2O$ + work up; then 2nd generation Hoveyda-Grubbs cat. (10 mol%), dry toluene, 80 ºC, 24 h. (iii) same as under (i). (iv) $SOCl_2$ (2 equiv), pyridine (5 equiv), $CH_2Cl_2$, 0 ºC, 2 h; then $H_2O$ at 0 ºC. See SI for further details.

We also studied the use of a trisubstituted VCC (**1n**). Despite the excellent regioselectivity, the enantiocontrol was significantly lower while producing the product with low diastereocontrol.[14] Finally, we used Hantzsch esters that would produce secondary radicals under the experimental conditions, leading to vicinal quaternary-tertiary carbons through a different route. In all these cases (**3ah**, **3ai** and **3aj**), the products were formed with high regiocontrol and *er* values adding further diversity to the developed methodology. The absolute configuration of the major enantiomer of compound **3ma** was determined to be (*R*) by X-ray diffraction.[15]

The synthesis of homoallylic alcohol **3ka** could be conveniently scaled up (10-fold) as shown in Scheme 4a. We then used **3aa** and **3ka** for product diversification studies (Scheme 4b). Hydroboration/oxidation of **3aa** provided access to 1,4-diol **4** in 72%; X-ray analysis revealed that the absolute configuration of the major enantiomer was (*S*).[15] A metathesis/cyclization of **3aa** in the presence of acryloyl chloride gave unsaturated lactone **5** (79%). Under similar reaction conditions as for **4**, the hydroboration/oxidation of **3ka** gave a Markovnikov type product (1,3-diol **6**, 94%)[16] as an approximate 2:1 mixture of diastereoisomers. Dehydration of **3ka** using thionyl chloride produced 1,4-diene **7** in 88% yield.

**Conclusion:** In summary, we here describe a Pd-mediated dual catalysis approach that allows for transformation of previously unreactive VCCs into chiral homoallylic alcohols featuring vicinal, highly congested carbon atoms. The developed protocol combines an atypical preference for the formation of branched regioisomers in a

sterically challenging allylic substitution event, and produces the products with enantiomeric ratios of up to 94:6. The present results mark a significant step forward in the use of modular VCCs in challenging enantioselective syntheses.

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(13) The oxidation of **2a** to its corresponding pyridine proceeds with a quantum yield of 7.5%, indicating that the coupling reaction proceeds immediately once the alkyl radicals are released using >90% of the radicals productively.

(14) Low diastereocontrol is a general phenomenon in the creation of vicinal quaternary/tetrasubstituted carbon stereocenters, see for instance ref. 3a and 3d.

(15) This configuration was determined for several crystals that were independently analyzed by X-ray diffraction, see the SI for details.

(16) The discrepancy between the hydroboration/oxidation of **3aa** and **3ka** is suggested to arise from a directing-group effect of the conformationally more restricted tertiary OH in **3ka**.