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RESEARCH ARTICLE

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Enantioselective Palladaelectro-Catalyzed C–H Activations by Transient Directing Groups: Expedient Access to Helicenes

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Abstract: Asymmetric palladaelectro-catalyzed C–H olefinations were achieved through the synergistic cooperation with transient directing groups. The electrochemical, atroposelective C–H activations were realized with high position-, diastereo-, and enantio-control under mild reaction conditions to obtain highly enantiomerically-enriched biaryls and fluorinated N–C axially chiral scaffolds. Our strategy provided expedient access to, among others, novel chiral BINOLs, dicarboxylic acids and helicenes of value to asymmetric catalysis. Mechanistic studies by experiment and computation provided key insights into the catalyst's mode of action.

Introduction

In recent years, organic electrosynthesis has undergone a remarkable renaissance, with notable advances in homogeneous electrocatalysis.[1] Significant momentum was particularly gained by the merger of electrosynthesis with organometallic C–H activation,[2] enabling the use of electrons as sustainable redox equivalents towards improved resource economy.[3] While major progress was thus represented by elegant studies from *inter alia* Jutand, and Mei *via* strong *N*-directing groups in palladium catalysis,[4] Ackermann,[5] Mei,[1a, 1g] Lei,[6] and Xu[7] among others, made progress towards electrochemical C–H activation using both *N*-chelation assistance[8] or weak *O*-coordination.[9] Despite these indisputable advances, full selectivity control in terms of enantioselective[10] electrochemical C–H activations[11] are thus far unfortunately unknown. This can be attributed to the major challenges in asymmetric metallaelectro-catalysis, including a) cathodic catalyst reduction, b) electrochemical degradation of chiral ligands, and c) unfavorable interactions of the electrolyte within the enantio-determining transition state. Hence, it is noteworthy that asymmetric electrochemical transformation[11] generally continue to be underdeveloped.[11,12]

Axially-chiral biaryls feature prominently as key structural motifs in privileged catalysts,[13] ligands,[14] and natural products[15] as well as in material sciences.[16] Since an early, albeit moderately selective report on rhodium(I)-catalyzed C–H alkylations of arylpyridines,[17] atroposelective syntheses of axially-chiral biaryls have been established, most notably by You,[18] Wencel-Delord/Colobert,[19] Yang[20] and Shi,[21] among others. In this context, Shi elegantly exploited transient directing groups for the synthesis of axially chiral biaryls.[22] Yet, despite of considerable progress, the synthesis of axially-chiral biaryls largely requires stoichiometric amounts of often toxic oxidants, which lead to the formation of undesired byproducts. In sharp contrast, enantioselective C–H activations that employ electricity as formal redox-equivalents are as of yet unprecedented. Within our program on sustainable C–H activation,[23] we have now unraveled the first electrochemical enantioselective synthesis of axially-chiral biaryls with the aid of a transient directing groups (TDG, Figure 1),[24] on which we report herein. Notably, our strategy set the stage for the assembly of highly enantio-enriched [n]helicenes. Additional salient features of our findings include a) first enantioselective electrochemical organometallic C–H activation, b) unprecedented use of transient directing groups in electrochemical C–H activations, c) electro-catalytic access to axially-chiral biaryls, d) mechanistic insights by computation e) assembly of N–C axially-chiral compounds, and f) late-stage diversification towards chiral BINOLs, helicenes and dicarboxylic acids.

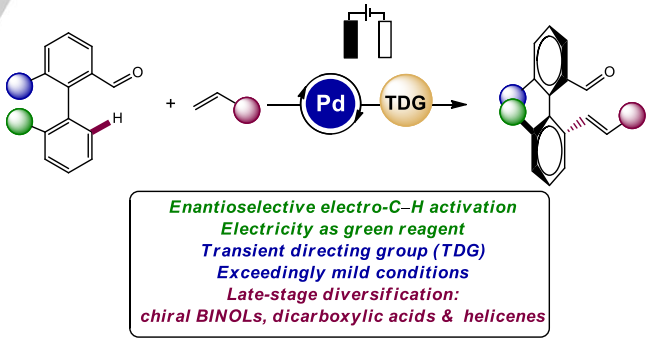


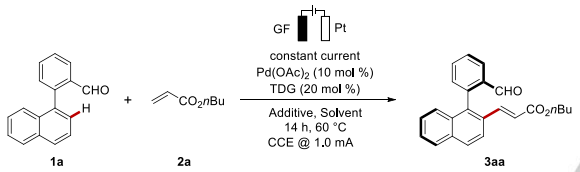
Figure 1. Enantioselective electrocatalytic C–H activation enabled by TDGs.

Results and Discussion

We initiated our studies by evaluating TDGs[24] for the envisioned atroposelective electrocatalyzed C–H olefination of biaryls **1a** with *n*-butyl acrylate (**2a**) (Table 1 and Table S-1 in the supporting information).[25] We were delighted to observe that initial experimentation with L-valine provided the desired olefinated product **3aa** indeed in 35% yield and 48% ee (entry 1). Initial optimization studies indicated that the redox mediator benzoquinone did not improve the performance. Probing

alternative TDGs failed to provide a significant improvement in chemical and optical yields (entries 2–6). Pleasingly, L-*tert*-leucine afforded a 53% yield with 97% ee (entry 7). Other electrolyte additives, such as NaOAc, KOAc, NaOPiv and nBu$_4$PF$_6$ showed inferior efficiency as compared with LiOAc (entries 8–11), emphasizing tight interplay of the additive serving both as electrolyte and for carboxylate-assisted strong bond cleavage (*vide infra*). Notably, other reaction media did not improve the catalyst's performance (entries 12–13). Slightly prolonging the reaction time delivered the desired product **3aa** with synthetically useful 71% yield and 97% ee (entries 14 and 15), while the metallaelectro-catalysis also occurred in the absence of air, albeit with reduced efficacy (entry 16). It is noteworthy that, in contrast to the use of chemical oxidants,[22e] a redox mediator was not required for efficient metallaelectro-catalysis. Control experiments confirmed the necessity of the TDG, the electricity and the palladium catalyst (entries 17–19).The mass balance was accounted for by unreacted starting material **1**.[25]

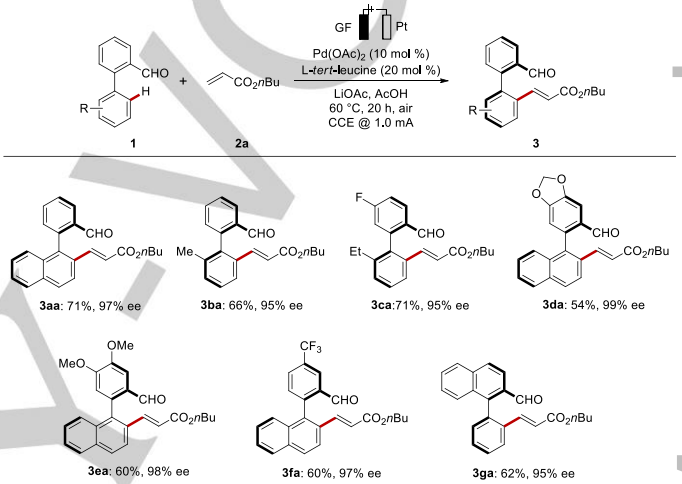
Table 1. Optimization of the atroposelective electrocatalyzed C–H olefination.[a]



Entry	TDG	Additive	Solvent	Yield [%]	*ee* [%]
1	L-valine	LiOAc	AcOH	35	48
2	L-phenylalanine	LiOAc	AcOH	43	18
3	L-proline	LiOAc	AcOH	47	20
4	L-aspartic acid	LiOAc	AcOH	23	28
5	L-tryptophan	LiOAc	AcOH	21	68
6	L-histidine	LiOAc	AcOH	45	24
7	L-*tert*-leucine	LiOAc	AcOH	53	97
8	L-*tert*-leucine	NaOAc	AcOH	47	99
9	L-*tert*-leucine	KOAc	AcOH	45	98
10	L-*tert*-leucine	NaOPiv	AcOH	50	96
11	L-*tert*-leucine	nBu$_4$PF$_6$	AcOH	48	99
12	L-*tert*-leucine	---	TFE	---	---
13	L-*tert*-leucine	---	TFE/AcOH	46	99
14[b]	**L-*tert*-leucine**	**LiOAc**	**AcOH**	**71**	**97**
15[b,c]	L-*tert*-leucine	LiOAc	AcOH	66	97
16[b,d]	L-*tert*-leucine	LiOAc	AcOH	43	97
17	---	LiOAc	AcOH	---	---
18[e]	L-*tert*-leucine	LiOAc	AcOH	25	97
19[f]	L-*tert*-leucine	LiOAc	AcOH	---	---

[a] Reaction conditions: Undivided cell, **1a** (0.20 mmol), **2a** (0.60 mmol), [Pd] (10 mol %), TDG (20 mol %), additive (2.0 equiv), solvent (4.5 mL), 60 °C, constant current at 1.0 mA, 14 h, graphite felt (GF) anode, Pt-plate cathode, isolated yields. [b] 20 h. [c] **2a** (2.0 equiv). [d] Under N_2. [e] Without electricity. [f] No palladium. TFE = 2,2,2-Trifluoroethanol.[25]

With the optimized reaction conditions in hand, we explored the versatility of the enantioselective palladaelectro-catalysis (Scheme 1). A number of biaryls containing electron-rich (**1d**, **1e**) and electron-withdrawing groups (**1f**) provided the desired axially chiral biaryls **3** with excellent enantioselectivities.



Scheme 1. Atroposelective electro-catalyzed C–H olefination of biaryls **1**.[25]

Next, a wide range of alkenes **2** was explored (Scheme 2). Here, fluoro- (**2i**), bromo- (**2j**), nitro- (**2k**) and carbonyl (**2l**) substituents on the arene were well tolerated in the electrochemical atroposelective C–H olefination, which should prove instrumental for further late stage modification. Moreover, vinyl sulfone (**2e)** and vinyl phosphonate (**2f**) were efficiently converted, delivering the desired products **3ae** and **3af**, respectively, with good yields and excellent enantioselectivites. The reaction proceeded likewise well with methyl vinyl ketone (**2g**) and acrylamide (**2m**) to furnish the axially chiral biaryls **3** with very high levels of enantio-induction.

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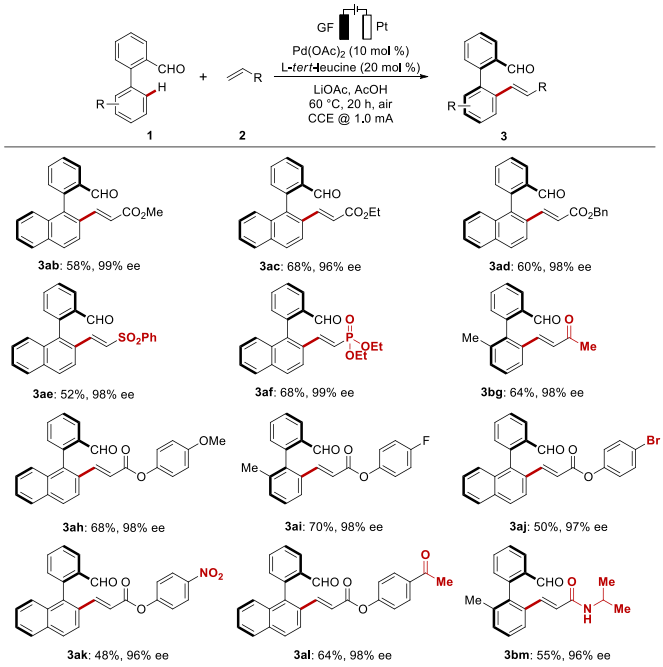
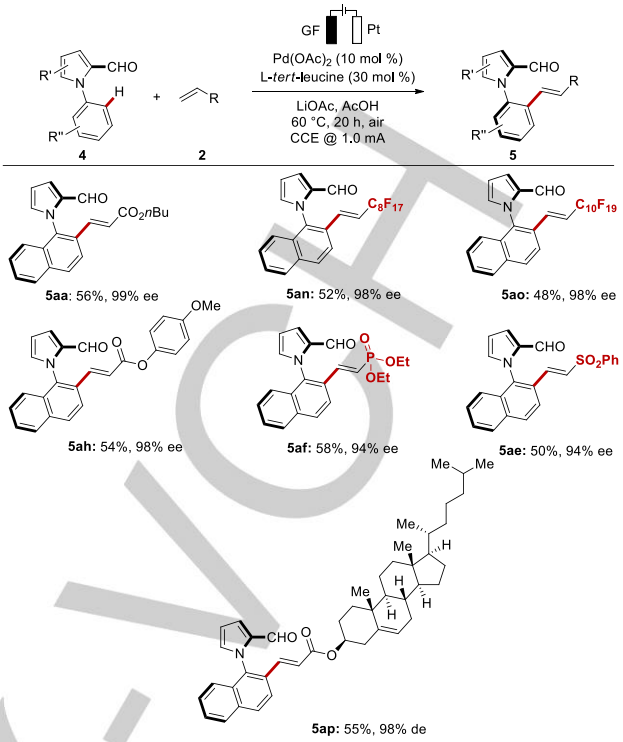


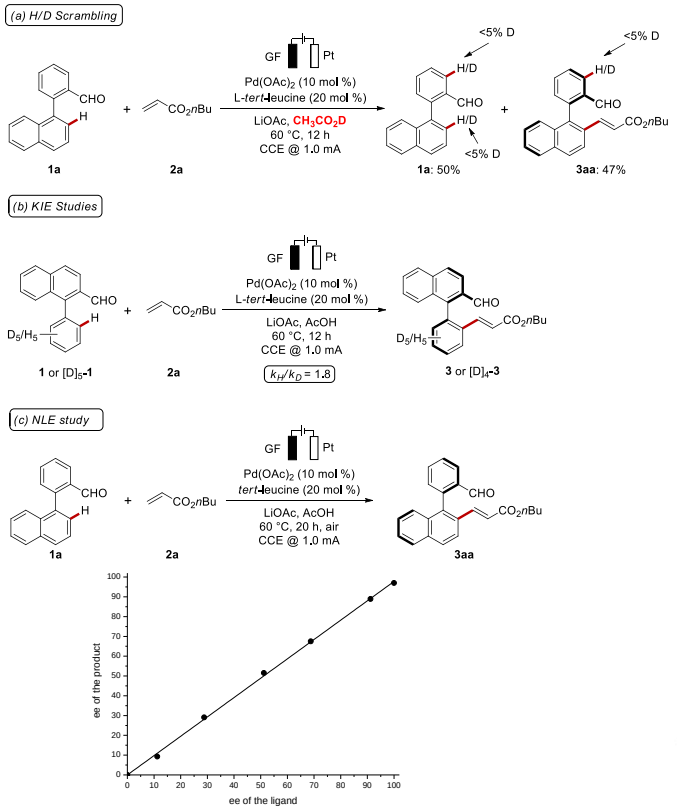
Scheme 2. Atroposelective palladaelectro-catalysis with alkenes **2**.[25]



Scheme 3. Atroposelective palladaelectro-catalyzed C–H olefination of *N*-aryl pyrroles.[25]

The palladaelectro-catalysis was not limited to the conversion of biaryls. Indeed, the strategy also set the stage for the synthesis of N–C[22a, 26] axially-chiral motifs by palladaelectro-catalysis. Under otherwise identical reaction conditions, we were able to access N–C axially-chiral *N*-aryl pyrroles in a site- and enantio-selective fashion. We were delighted to realize unprecedented C–H perfluoroalkenylations in a highly enantioselective fashion to deliver the synthetically useful axially-chiral fluorinated heterobiaryls **5an**-**5ao**. Likewise, vinyl sulfone (**5ae**), vinyl phosphonate (**5af**) and cholesterol derivative (**5ap**) mirrored the versatility towards N–C axially chiral scaffolds (Scheme 3).

Intrigued by the outstanding efficacy of the atroposelective palladaelectro-catalyzed C–H activation, we became attracted to unravelling its mode of action. First, H/D scrambling was not observed when AcOD was used as the reaction media (Scheme 4a). Second, kinetic studies with isotopically-labeled substrates revealed a KIE value of ≈1.8 (Scheme 4b). These experiments are suggestive of the C–H activation being the rate-determining step. Third, we did not observe a non-linear-effect (NLE), being indicative of the enantio-determining step involving a metal to ligand ratio of 1:1 (Scheme 4c).



Scheme 4. Summary of key mechanistic findings.

Subsequently, we probed the catalyst's mode of action by means of computational studies at the PW6B95-D4/def2-TZVP+SMD(AcOH)//PBE0-D3BJ/def2-SVP level of theory (Figure 2).[25] A detailed analysis of the C–H activation process revealed that the intermediate that leads to the formation of the seven-membered intermediate I-1^7 is 12.0 kcal mol^{-1} more favorable than the formation of the five-membered intermediate I-1^5. Interestingly, this stabilization is dominated by attractive non-covalent interactions between the *tert*-butyl group of the TDG and the substrate's naphthalene moiety as well as the arene π-system and the palladium (Figure 3). These secondary dispersive forces thus allow for a favorable square-planar coordination geometry. The migratory insertion of the alkene gives preference to the formation of the linear product in lieu of the branched product by 4.7 kcal mol^{-1} (TS4-5).

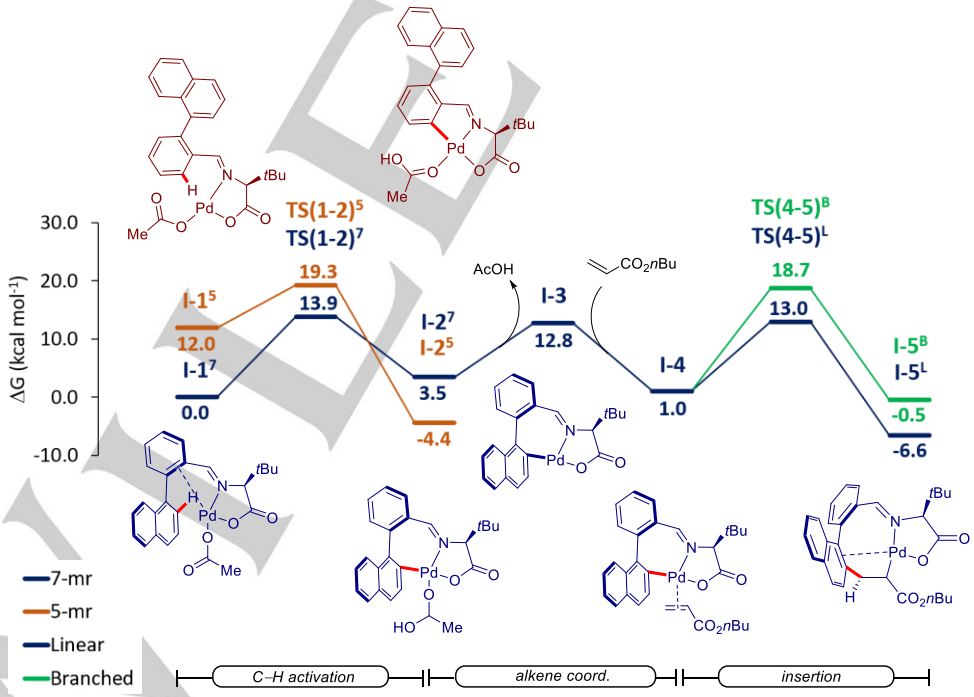


Figure **2**. Computed relative Gibbs free energies ($\Delta G_{333.15}$) in kcal mol^{-1} for the key C–H activation and β-H elimination elementary steps at the PW6B95-D4/def2-TZVP-SMD(AcOH)//PBE0-D3BJ/def2-SVP level of theory. Superscripts 5 and 7 relate to structures, which lead to the formation of the 7-membered *versus* the 5-membered cyclometallated intermediates. B and L correspond to the branched and linear products.

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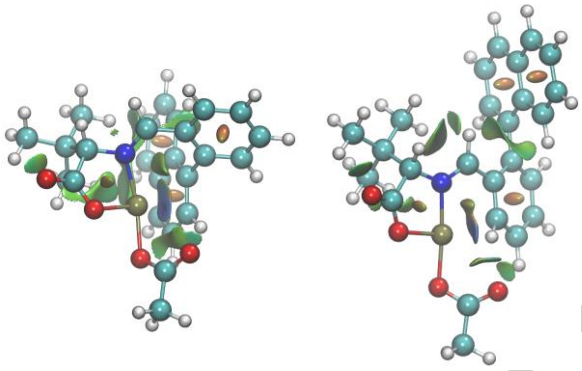
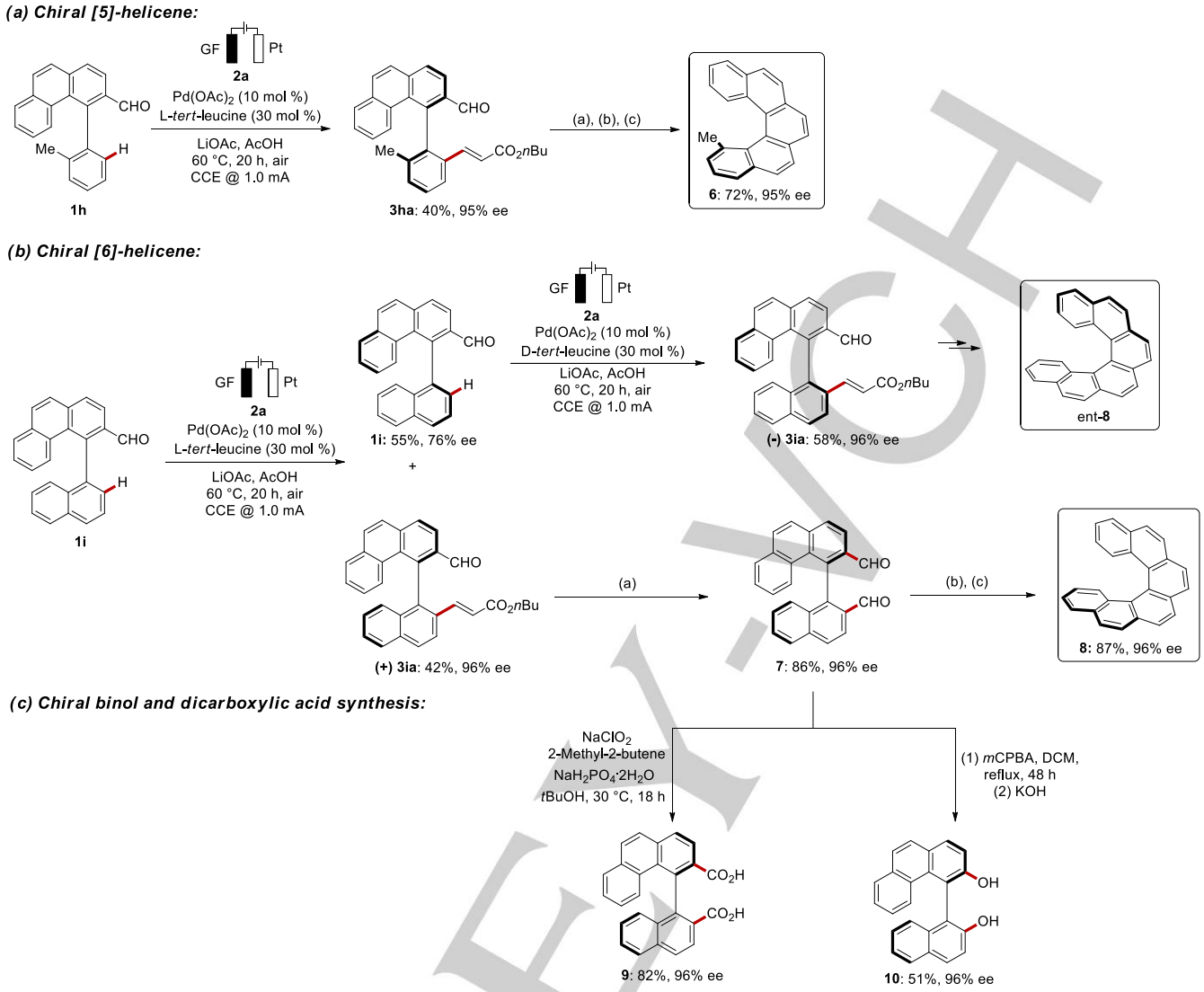


I-1^7 **I-1^5**

Figure **3**. Visualization of the non-covalent interactions calculated with the help of the NCIPLOT program, for the intermediates I-1^7 and I-1^5. In the plotted surfaces, red correspond to strong repulsive interactions, while green and blue correspond to weak and strong attractive interactions, respectively.

Finally, we explored the late-stage diversification of the thus-obtained highly enantiomerically-enriched biaryls towards chiral helicene. While significant advances in the synthesis of chiral helicenes have been noted,[27] asymmetric C–H activation-based electrocatalysis has thus far not been employed in the assembly of enantiopure helicenes. Upon performing a kinetic resolution on conformationally stable aldehyde **1h** under the optimized reaction condition, the olefinated product **3ha** was obtained with 95% ee. Further modification provided the [5]helicene **6** with overall high chemical and optical yield (Scheme 5a). The synthesis of [6]helicene **8** and [6]helimers *ent*-**8** was accomplished likewise. The recovered starting material **1i** was next submitted to the asymmetric palladaelectro-catalysis, giving the other enantiomer (-)**3ia** with 96% ee (Scheme 5b). The synthetic utility of our approach was further reflected by providing the chiral dialdehyde **7**. Dialdehyde **7** was itself converted through a Pinnick oxidation into chiral dicarboxylic acid **9**, whilst Baeyer-Villiger-oxidation gave the chiral BINOL **10** (Scheme 5c). These new chiral molecules should find multiple applications as privileged ligands for asymmetric catalysis.



Scheme 5. Electrochemical access to chiral Helicenes. (a) $K_2OsO_4 \cdot 2H_2O$ (15 mol %), $NaIO_4$ (10 equiv), THF/H_2O (2/1), 50 °C, 24 h; (b) $MePPh_3Br$ (3.8 equiv), *n*BuLi (3.2 equiv), THF, -78 °C to rt, 1 h; (c) Grubbs II (10 mol %), CH_2Cl_2, MW, 95 °C.

Conclusion

In summary, we have reported on the first asymmetric metallaelectro-catalyzed C–H activation. The atroposelective organometallic C–H activation was realized by a transient directing group manifold. The palladelectro-catalysis was characterized by high enantioselectivites under mild reaction conditions[28] for the synthesis of enantioenriched axially-chiral biaryls and heterobiaryls being devoid of chemical oxidants. Experimental, kinetic and computational studies on the metallaelectro-catalysis unraveled key elements of the catalyst's working mode. Our strategy also set the stage for the efficient assembly of novel enantio-enriched BINOLs, dicarboxylic acids and helicenes.

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Keywords: asymmetric C–H activation • biaryls • electrochemistry • helicene • palladium • transient directing group

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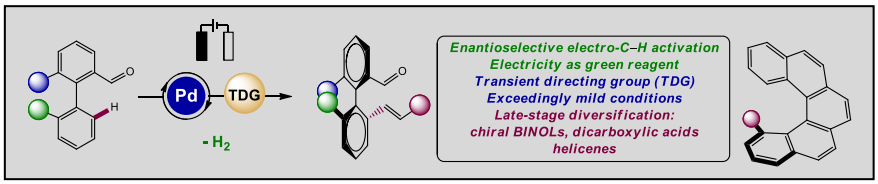

EE: ***E***nantioselective ***E***lectro-catalysis was realized in terms of asymmetric C–H activation through transient directing group (TDG)-enabled palladaelectro-catalysis. Experiments and calculations rationalize the key transition states, while the asymmetric electrocatalysis provided step-economical access to axially-chiral bi(hetero)aryl diols, diacids and helicines.

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