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Dearomatization

Palladium-Catalyzed Enantioselective Three-Component Dearomative Coupling of Bromoarenes: Modular Construction of Terpenoid Scaffolds

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Abstract: We report a palladium-catalyzed asymmetric three-component coupling of bromoarenes, diazoalkanes, and malonates. It represents a significant advancement in catalytic enantioselective dearomative 1,4-difunctionalization of unactivated arenes. A palladium catalyst of a novel phosphoramidite enables a domino reaction consisting of enantiofacial aryl insertion of a bound diazoalkane and regioselective and stereospecific allylic substitution. The new reaction was readily applied in short total syntheses of three terpenoids, including (+)-erogorgiaene, (−)-7-hydroxy-3,4-dihydrocadalin, and (−)-odongrossin C. Mechanistic studies establish that stereocontrol arises from a concerted aryl migration/N_2 extrusion, which forms the key cyclic π-allyl palladium intermediate. The C4-regioselectivity of the malonate attack is governed by a combination of ligand effects, silyl group sterics, and stabilizing noncovalent interactions between the naphthyl ring and sodium malonate.

Introduction

In recent decades, catalytic asymmetric dearomatization (CADA) of simple arenes has emerged as an efficient strategy for constructing complex motifs that are present in various bioactive natural products and pharmaceuticals.[1–5] However, most CADA reactions rely on electron-rich indole, phenol, and electron-deficient heteroarenes to achieve good chemo-, regio-, and enantioselectivities.[6–35] On the other hand, examples of CADA transformations of unactivated arenes such as naphthalene and benzene remain limited due to high reaction barriers and difficulty in addressing these issues of these selectivities.[36–39] For example, You reported a pioneering work on asymmetric 1,4-difunctionalization of naphthalene that was initiated by Pd-catalyzed intramolecular allylic alkylation (Figure 1a, A-1).[40] Similarly, Jia, Zhang, and You disclosed CADA examples that were initiated by palladium-catalyzed intramolecular Heck cyclization (Figure 1a, A-2).[41–43] Trost et al. have reported an intermolecular palladium-catalyzed asymmetric dipolar cycloaddition of nitroarenes, giving two examples of fused bicyclic products (Figure 1a, A-3).[44] Recently, Sarlah[45–48] and You[49,50] employed visible light-induced triplet states to overcome high reaction barriers of unactivated arenes,[51–53] producing 1,4-*cis*-disubstituted dearomative products. Despite these remarkable achievements, there is a need for innovative methods for intermolecular enantioselective CADA reactions of common arenes, which produce useful motifs that are difficult to synthesize from other methods.[54–56]

Previously, Bao and Yamamoto reported that η^3-benzyl palladium species, which were produced through oxidative addition of palladium(0) to benzylic chloride, led to dearomatization of the arene after nucleophilic attack by allyltributylstannane or stabilized enolates.[57–65] More recently, Yamaguchi and Muto demonstrated palladium-mediated conversion of bromoarenes and alkyl carbene precursors to benzylic palladium(II) complexes, leading to dearomative products in racemic forms.[66–69] Nevertheless, two main challenges need to be addressed: achieving high enantiofacial selectivity in intermolecular aryl insertion to the palladium carbene complexes producing chiral benzylpalladium species and achieving remote selectivity in subsequent dearomative transformation of palladium π-allyl species.[70]

Several challenges arise from the need to meet disparate ligand requirements in two stereoselective steps in a catalytic cycle: a chemo-, regio-, and enantioselective generation of chiral η^3-benzyl Pd(II) complex **B-5** and its subsequent regio-, and enantioselective transformation by nucleophiles (Figure 1b). Pd-mediated premature couplings of aryl halides and nucleophiles are also foreseeable side reactions.[71,72] Additionally, dearomatized products may undergo rapid rearomatization under acidic or basic conditions.[60,63]

Our interest in developing asymmetric dearomative transformation of unactivated arenes[73–75] prompted us to explore enantioselective reaction manifolds featuring η^3-allyl

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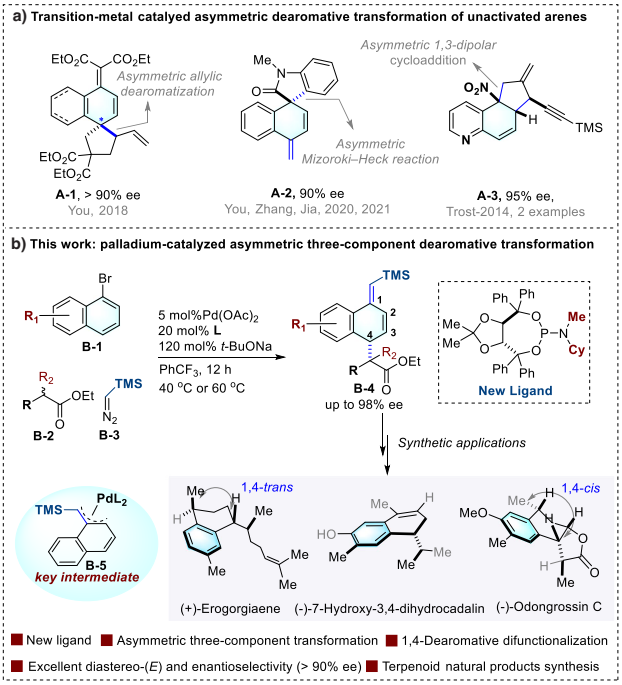

Figure 1. a) Representative examples of asymmetric dearomative transformations of functionalized arenes. b) Palladium-catalyzed asymmetric three-component dearomative couplings of bromoarenes (this work).

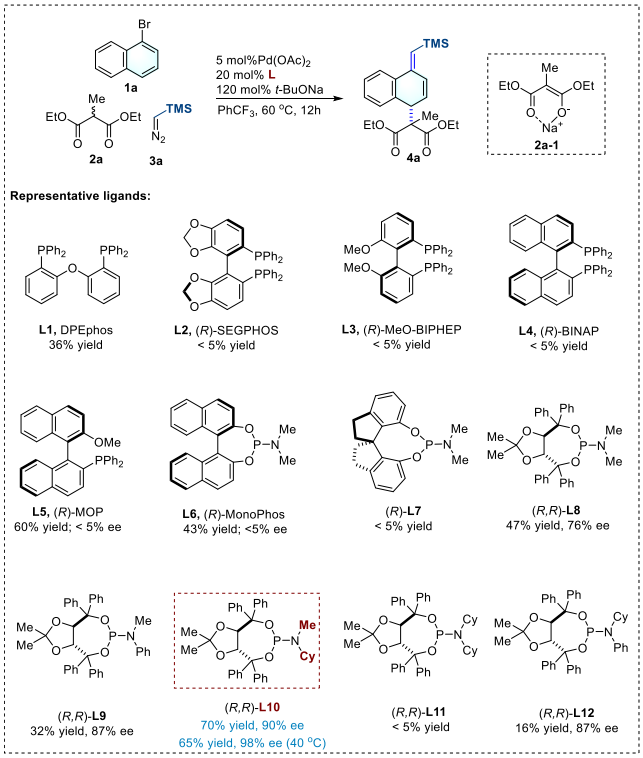

Figure 2. Ligands effect.

palladium(II) species. Herein, we present our findings that a palladium catalyst of a new monodentate phosphoramidite derived from TADDOL facilitates palladium-catalyzed dearomative three-component transformation of 1-bromonaphthalenes, diazoalkanes, and manolates with excellent regio-, diastereo-, and enantioselectivity. The resulting products serve as versatile precursors for the synthesis of both *cis*- and *trans*-1,4-disubstituted hydrogenated naphthalenes (DHNs), important structural motifs found in numerous bioactive terpenoids; notably, these diastereoisomers have traditionally been challenging to access through conventional synthetic methods.[76] Furthermore, we successfully synthesized three natural products of (+)-erogorgiaene, (−)-7-hydroxy-3,4-dihydrocadalin, and (−)-odongrossin C using the new dearomative CADA reaction as the key step.

Results and Discussion

Optimization of Reaction Conditions

Our research began with a model reaction of 1-bromonaphthalene (**1a**), α-methyl malonate (**2a**), and $TMSCHN_2$ (**3a**). *t*-BuONa was used to ensure efficient generation of the putative enolate. As depicted in Figure 2, DPEphos (**L1**) and $Pd(OAc)_2$ gave the desired dearomative product **4a** in 36% yield. We then examined a range of chiral diphosphines. Unfortunately, commonly used (*R*)-SEGPHOS, (*R*)-MeO-BIPHEP and (*R*)-BINAP were unable to produce the desired product **4a** (Table S1). When (*R*)-MOP was used, the desired product **4a** was obtained with a 60% yield, but in <5% ee. Interestingly, the use of phosphoramidite (*R*)-MonoPhos **L6** resulted in 43% yield, but in poor ee. Next, two phosphoramidites **L7** and **L8** derived from (*R*)-1,1′-spirobiindane-7,7′-diol and (*R*,*R*)-TADDOL, respectively, were synthesized and subjected to the model reaction (for details see Supporting Information). To our delight, ligand **L8** delivered product **4a** with 47% yield and 76% ee, while **L7** gave a trace amount of **4a**. Thus, we used (*R*, *R*)-TADDOL backbone for further ligand optimization.[77–79] When one *N*-methyl group was replaced by a phenyl ring (**L9**), the yield decreased to 32% but the selectivity increased to 87% ee. Finally, **L10** having an *N*-cyclohexyl ring instead phenyl resulted in a satisfactory 70% yield and excellent 90% ee. When the reaction was conducted at 40 °C, 65% yield and 98% ee were obtained (Table S4). Conversely, ligand **L11** bearing *N,N*-dicyclohexyl rings and ligand **L12** having a *N*-cyclohexylaniline group gave low yields of **4a**, suggesting that the steric element in the phosphoramidite plays a crucial role in the catalytic performance, probbaly in the step of the aryl insertion to putative palladium carbene species (see below).

In the examination of reaction solvents, polar solvents such as THF, 1,4-dioxane, and DMF did not give the desired product (Table S2). On the other hand, nonpolar solvents like toluene, DCM, and *m*-xylene produced the product **4a**, albeit in decreased yields and lower ees (Table S2). The use of *t*-BuONa as the base was essential for the transformation, while *t*-BuOLi and *t*-BuOK did not deliver the desired product **4a** (Table S3). The use of NaH as the base afforded the desired product in 53% yield and 90% ee (Table S3). However, the rearomatized derivative of **4a** was formed due to the

excess base. When *pre*-formed sodium malonate (**2a-1**) was employed, the enantioselectivity remained high (94% ee), but the yield dropped to 46%, likely owing to its hygroscopic nature and sensitivity to moisture during reaction setup (Table S7). Consequently, *t*-BuONa was selected as the optimal base for all subsequent experiments. Screening of palladium sources showed that $Pd(OAc)_2$ was the best choice (Table S5). Further experiments on ligand loading indicated that a ligand loading of 20 mol% is crucial for achieving good yields, as it enables effective coordination of the palladium catalyst (5 mol%) (Table S6). Thus, we established an optimal condition consisting of 5 mol% of $Pd(OAc)_2$, chiral ligand **L10**, and *t*-BuONa in $PhCF_3$ solvent.

Substrate Scope

In our investigation of naphthyl halides, 1-chloronaphthalene gave very low conversion under standard conditions, while 1-iodonaphthalene mainly produced the enolate α-arylation product (Table S). Therefore, we subsequently evaluated the substrate scope of 1-bromonaphthalenes containing various substituents (Figure 3a). The aryl bromide bearing a 7-phenyl substituent produced the desired product in excellent 93% ee and good 62% yield (**4b**).

An analogous substrate having a 7-cyclohexyl group gave the product in excellent 90% ee and a slightly lower 56% yield (**4c**). Both substrates, having an electron-donating 7-MeO (**4d**) and an electron-deficient 7-F substituent (**4e**), produced the desired products in good yields and excellent ee values. The substrate bearing an aryl chloride afforded the product in 89% ee (**4f**) and 55% yield due to the competitive side reaction of the C─Cl bond. Substrates with substituents at the 6-position were then studied, and both electron-donating and withdrawing substituents were well tolerated (**4i-4o**), while a substrate bearing 6,7-disubstituents gave the desired product in 84% ee and 52% yield (**4h**). Notably, substrates containing a methyl ketone (**4k**) and unprotected amidic *N*-H (**4m**) still afford the desired products in good results under the basic reaction conditions.

The naphthyl bromides containing substituents at other positions were explored in details. The substrate bearing 2-methyl group produces a mixture of the *E*/*Z* isomers (1.5:1) (**4p**) in good 73% yield, while a substituent at the 3-position may obstruct the nucleophilic reaction of the malonate, leading to the formation of the product in a 52% yield (**4q**). Substrates with substituents at the 8-position gave trace amounts of the product with most of the starting material recovered, owing to the steric hindrance (**4r**). A 5-methyl group may have reduced the efficiency of the allylic substitution, but the desired product was still generated in 50% yield and good 81% ee (**4s**). Additionally, 2-bromothiphene proved to be also a good substrate for the three-component transformation in a slightly lower selectivity of 82% ee (**4t**). However, the introduction of a 3-phenyl group significantly compromised enantiocontrol, resulting in moderate 40% ee (**4u**). Additionally, 4-bromobenzofuran also produced the dearomative product, but the product was prone to fast rearomatization (**4v**). Unfortunately, we found that bromobenzene (**4w**), 3-bromopyridine (**4x**), 2-bromonaphthalene and electron-deficient 5-bromoisoquinolone did not give satisfactory results (Table S8).

The representative nucleophiles (Figure 3b) included diethyl α-methyl malonate, di-*i*-propyl (**5a**), di-*n*-butyl (**5b**), and dibenzyl malonate (**5c**), all producing desired products in good yields and excellent ees. Malonates having α-benzyl (**5d**) and α-*n*-propyl substituents (**5e**) reacted well, too. Methyl α-cyanopropanoate affords 80% yield of **5f** in a 1:1 ratio of two diastereomers (88% ee and 84% ee); *t*-butyl α-cyanopropanoate gives two diastereomers in a 3.5:1 ratio (82% yield and 81% ee for the major isomer). However, α-methyl malononitrile failed to give the desired product. Reactions with other commercially available diazo reagents, such as ethyl 2-diazo-2-phenylacetate, ethyl 2-diazoacetate, and diethyl 2-diazomalonate, were unsuccessful, leaving most of the aryl bromide starting materials unreacted. (Table S9). Conversely, we found that the *N*-tosylhydrazone derived from *p*-tolualdehyde served as an effective diazo precursor under elevated temperature (60 °C),[80–82] affording the 1,4-difunctionalized product 5h in 48% yield with 82% ee (Figure 3c).

Derivatization of 1,4-Disubstituted Hydrogenated Naphthalenes (DHNs)

After evaluating a representative array of substrates, we commenced the diversification of 1,4-DHN derivatives (Figure 4a). These derivatives are core motifs of many bioactive terpenoids; for instance, 1,4-*cis*-DHNs are core units in many cadinane-type terpenoids,[83,84] whereas 1,4-*trans*-DHNs are present in serrulatane and amphilectane-type terpenoids.[85–88] Initially, we focused on selectively hydrogenating the 1,3-diene of **4d** and successfully obtained 1,4-*cis*-DHN **6a** in exclusive *cis*-diastereoselectivity under classic hydrogenation over Pd/C. The malonate was subsequently reduced by $LiAlH_4$ to afford diol **6b** in 92% yield. The absolute structure of *S*-**6b** was determined by single-crystal X-ray diffraction, which helped us to set the absolute configurations of other products from the catalytic couplings. Alternatively, the exocyclic olefin in **4d** was reduced by potassium diazodicarboxylate, giving 1,4-*cis*-product **6c** predominantly.

The reduction of dienes predominantly gave the 1,4-*cis*-products owing to the steric factor of the malonate (see Table S7). Therefore, we decided to explore other methods to selectively access 1,4-*trans*-DHNs. Pd/C poisoned with quinoline thus enabled a partial 1,4-reduction to give an internal alkene, and subsequent desilylation by HF gave product **6d** in 82% yield over two steps. Subsequently, the olefin of **6d** was converted to an epoxide using *m*-CPBA and epoxide opening with hydrogenolysis over Pd/C with NaOH as an additive[89] afforded 1,4-*trans*-DHN **6e** as the major product. Importantly, the hydroxyl group in **6e** can act as a handle for further diversification. The efforts to diversify 1,4-DHNs proved to be valuable for the practical synthesis of natural compounds featuring *cis*- or *trans*-1,4-DHN motifs (Figure 4a).

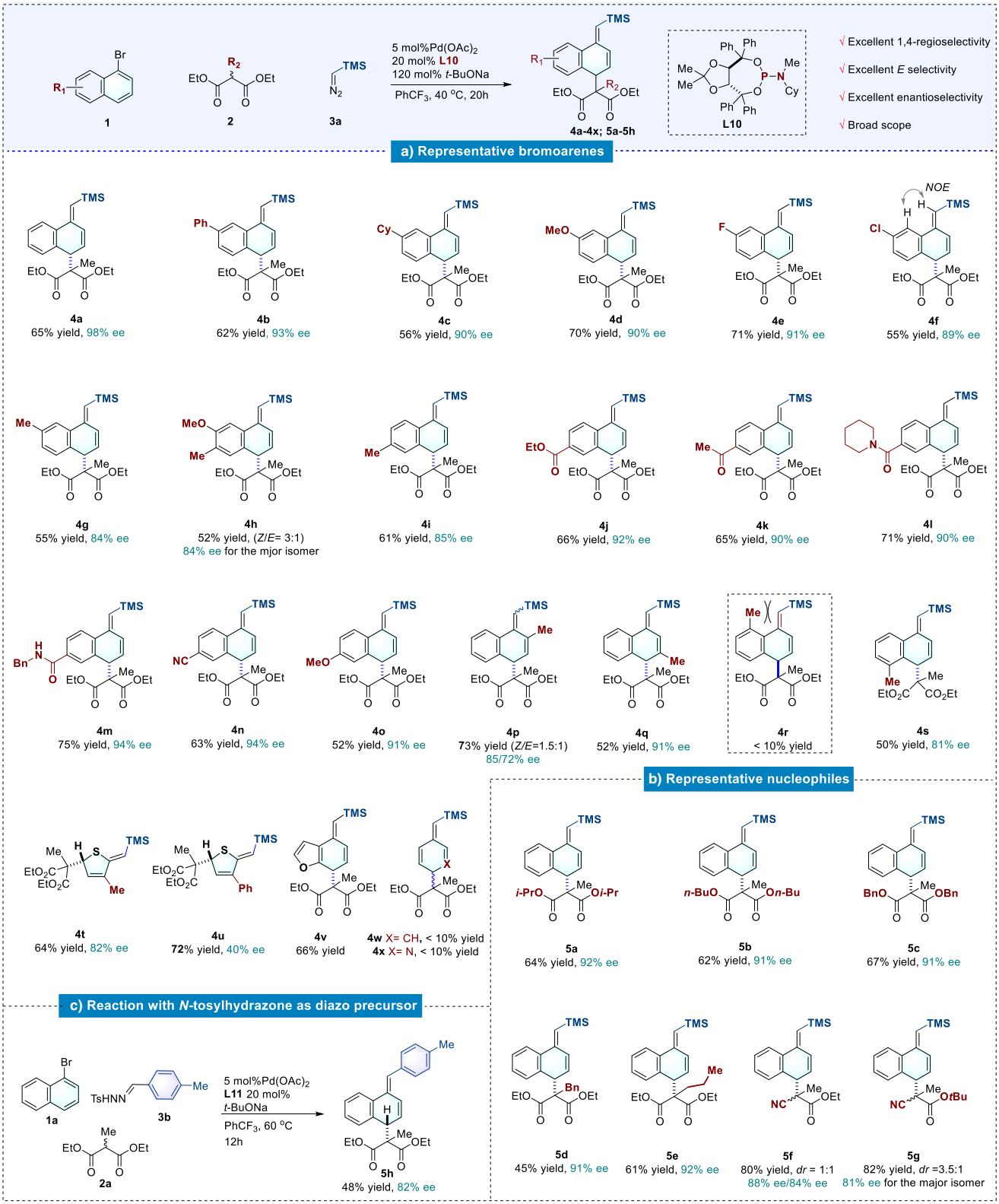

Figure 3. Substrate scope: a) bromoarenes, bromothiophenes, and benzofuran; b) malonates and α-cyanopropanoates; c) *N*-tosylhydrazone as diazo precursor.

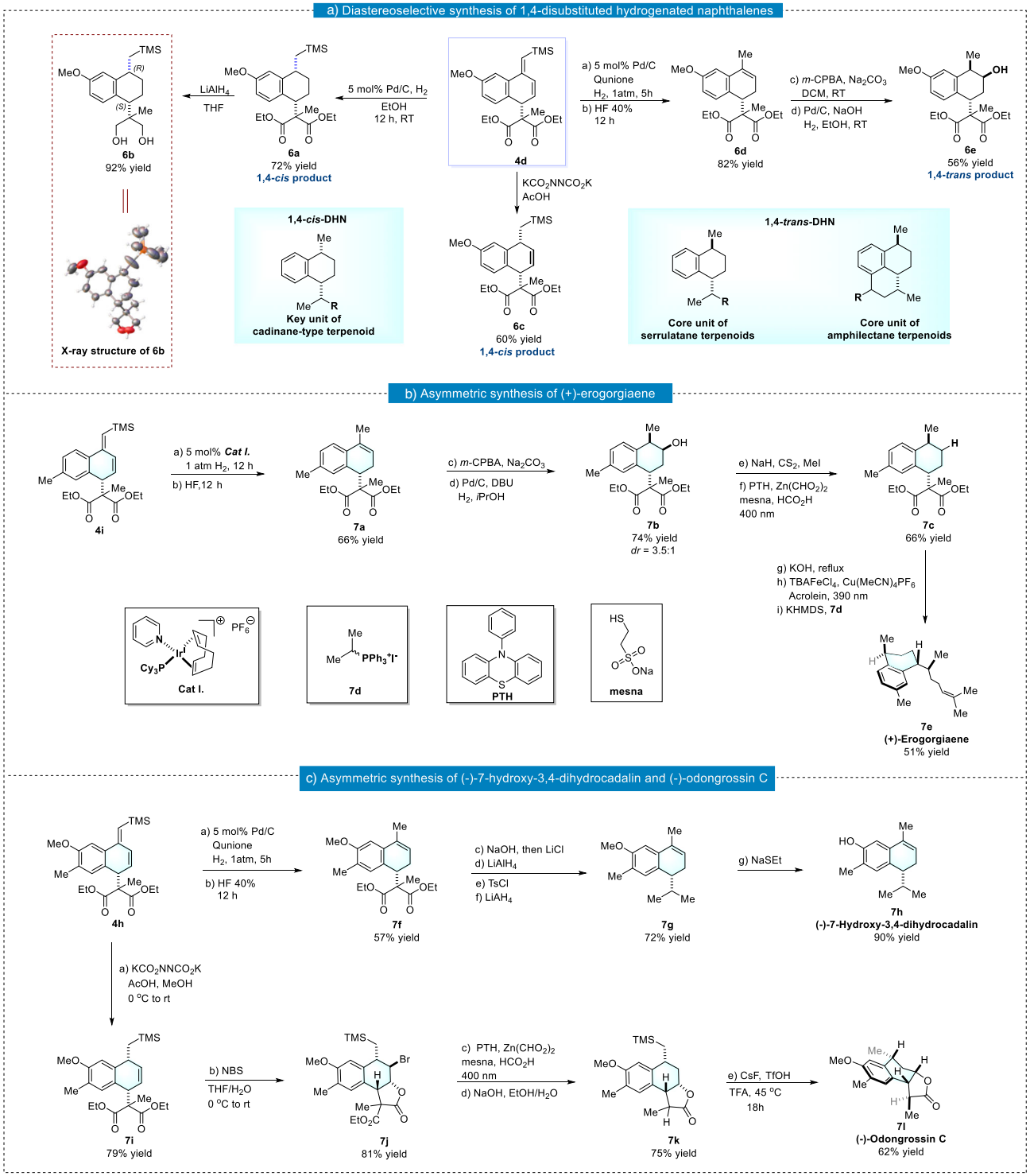

Figure 4. Synthetic applications. a) Diastereoselective synthesis of 1,4-disubstituted hydrogenated naphthalene (DHN). b) Asymmetric synthesis of (+)-erogorgiaene. c) Asymmetric synthesis of (−)-7-hydroxy-3,4-dihydrocadalin and (−)-odongrossin C.

Asymmetric Synthesis of Natural Products

Marine natural products derived from soft coral *Pseudopterogorgia elisabethae* have attracted significant pharmaceutical interest for decades, owing to their remarkable biological activities. Characteristic pseudopterosin compounds typically incorporate a 1,4-*trans*-DHN structural motif, exemplified by (+)-erogorgiaene,[90,91] which exhibits promising anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv. In recent decades, many research groups have devised various synthetic routes for the rapid production of these bioactive compounds for pharmaceutical

development.[92–96] In contrast, Chinese liverwort-derived cadinanes generally feature a 1,4-*cis*-DHN scaffold.[97] Building upon our asymmetric three-component dearomative transformation, we have prepared these terpenoids with high efficiency and stereocontrol.

(+)-Erogorgiaene presents two synthetic challenges: precise assembly of the 1,4-*trans*-DHN core and stereoselective introduction of the alkyl side chain.[92–96] As outlined in Figure 4b, we initiated our synthesis from compound **4i**. A selective 1,4-reduction of the diene using Crabtree catalyst followed by TBAF desilylation delivered intermediate **7a** in 66% yield. Subsequent epoxidation and palladium-catalyzed reductive ring-opening containing DBU additive afforded 1,4-*trans*-product **7b** in 74% yield and *dr* 3.5:1 (Table S11). Following Wickens' protocol,[98] visible-light-induced deoxygenation of **7b** provided diester **7c** in 68% yield. Basic hydrolysis of the malonate generated a monocarboxylic acid, which served as an alkyl precursor in Zeng's photocatalytic coupling with acrolein.[99] The resultant aldehyde was subjected to Wittig olefination to furnish the terminal alkene. This three-step sequence with an overall yield of 51% thus delivered (+)-erogorgiaene **7e** with NMR spectra matching those in the literature (Table S12). Notably, this synthesis of (+)-erogorgiaene was accomplished in ten steps with an overall yield of 11% from commercially available 6-methyl-1-bromonaphthalene. Remarkably, the synthesis required only five chromatographic separations and avoided harsh reaction conditions, making it particularly competitive for scale preparation of (+)-erogorgiaene.

Next, we accomplished asymmetric total syntheses of two cadinane-type terpenoids, (−)-odongrossin C featuring a 1,4-*cis*-DHN unit and (−)-7-hydroxy-3,4-dihydrocadalin. These structurally related natural products share a distinctive 6-methoxy-7-methyl-1,4-DHN core. Despite their promising biological profiles, chemical synthesis to access these compounds had remained elusive to date. We decided to employ a divergent synthesis of both targets from a common intermediate **4h,** which was assembled via our asymmetric three-component transformation (Figure 4c). For (−)-7-hydroxy-3,4-dihydrocadalin, which has antifungal activities, our synthesis commenced with a 1,4-reduction of the diene using Crabtree's catalyst, followed by HF desilylation to afford **7f**.

Subsequent transformations included: selective basic hydrolysis of one ester of malonate; $LiAlH_4$ reduction of the remaining ester to a primary alcohol; tosylation and hydride reduction to give **7g** in 72% yield over four steps. Finally, NaSEt promoted demethylation to complete the synthesis of **7h** in an overall yield of 19% (8 steps from 1-naphthyl bromide).

The preparation of (−)-odongrossin C included 1,2-selective reduction of diene **4h** to afford *cis*-**7i** in 79% yield, followed by diastereoselective bromoesterification to afford **7j** as a single diastereomer. Subsequent photocatalytic debromination and basic hydrolysis delivered **7k** in 75% yield in two steps, with final desilylation under Zhao's conditions[100] providing **7l** in 62% yield (in an overall yield of 15% over 6 steps). The NMR spectra of both synthetic products match perfectly with those in the literature (Tables S13 and S14).

Mechanistic Investigations

To gain detailed insight into the enantio- and regioselectivity of this transformation, we performed density functional theory (DFT) calculations at the SMD-B3LYP-D3(BJ)/def2-TZVP//B3LYP-D3(BJ)/def2-SVP level to determine the minimum-energy reaction pathway (MERP),[101–103] mainly to probe the origin of the enantioselective aryl insertion to Pd-bound $N_2CHSiMe_3$ and to determine the origin of terminal C4 regioselectivity in final allylic substitution. In our DFT studies, we selected aryl Pd(II) **INT1** as starting point (Figure 5a). The aryl migration of **INT1** proceeds via a concerted aryl migration/N_2 extrusion pathway (Fig. S17) with a bound $N_2CHSiMe_3$ is highly exergonic due to extrusion of dinitrogen.[104–107] The process may proceed via two competing intermediates among the eight possible intermediate conformers, **INT2** and **INT2'**, differing in *syn* or *anti* orientation of the Pd-naphthyl ring and the amide fragment of **L10** on the Pd center. Calculations revealed that *anti* transition state **TS1-1** was 4.7 kcal mol^{-1} more stable in Gibbs free energy than *syn* **TS1-3**, primarily due to avoidance of steric repulsion between the aryl and amide units of ligand. This explains the importance and judicious choice of the amide fragment with a delicate balance of size in the optimal phosphoramidiate ligand. Thus, the stereoselective aryl insertion to the bound diazo compound and concomitant extrusion of N_2 via **TS1-1** is favored, forming a TMS-substituted η^3-benzyl complex **INT3** (Figure 5b-I). Notably, the enantioselectivity of the final product in this domino transformation is determined at this step. Then **INT3** isomerized to INT**4** which is less favorable in energy.[60,104,105] Both **INT3** and **INT4** can serve as active intermediates for malonate attack through distinct pathways, and we have computed five possible transition states (Figure 5a). Among these, **TS6** (−31.5 kcal mol^{-1}) exhibits the lowest energy among the TSs we examined, favoring terminal outer-sphere nucleophilic substitution to afford the experimentally detected (S)-**4a**. Notably, **TS4** corresponds to an inner-sphere attack of a Pd-bound malonate previously suggested by Yamaguchi and Muto,[66–69] but it has a much higher energy (−20.5 kcal mol^{-1}) and leads to the "wrong" enantiomer; thus, it is discounted (Figure 5b-II).

The DFT results reveal that **INT4** undergoes allylic substitution preferentially at the distal C4 position (via **TS6**, $\Delta G^{\#} = -31.5$ kcal mol^{-1}) rather than at the C2 site (via **TS5**, $\Delta G^{\#} = -22.9$ kcal mol^{-1}). The large energy difference (8.6 kcal mol^{-1}) thus strongly favors the C4 attack, leading to exclusive formation of (*S*)-**4a** as the final product. This pronounced regioselectivity arises from two key factors: steric repulsion of the TMS group that blocks the C2 position, and attractive noncovalent interactions between the naphthalene moiety and sodium malonate.[108] In addition, DFT calculations were performed to evaluate the interaction between solvent $PhCF_3$ and sodium malonate. The results confirm that benzotrifluoride does not perturb

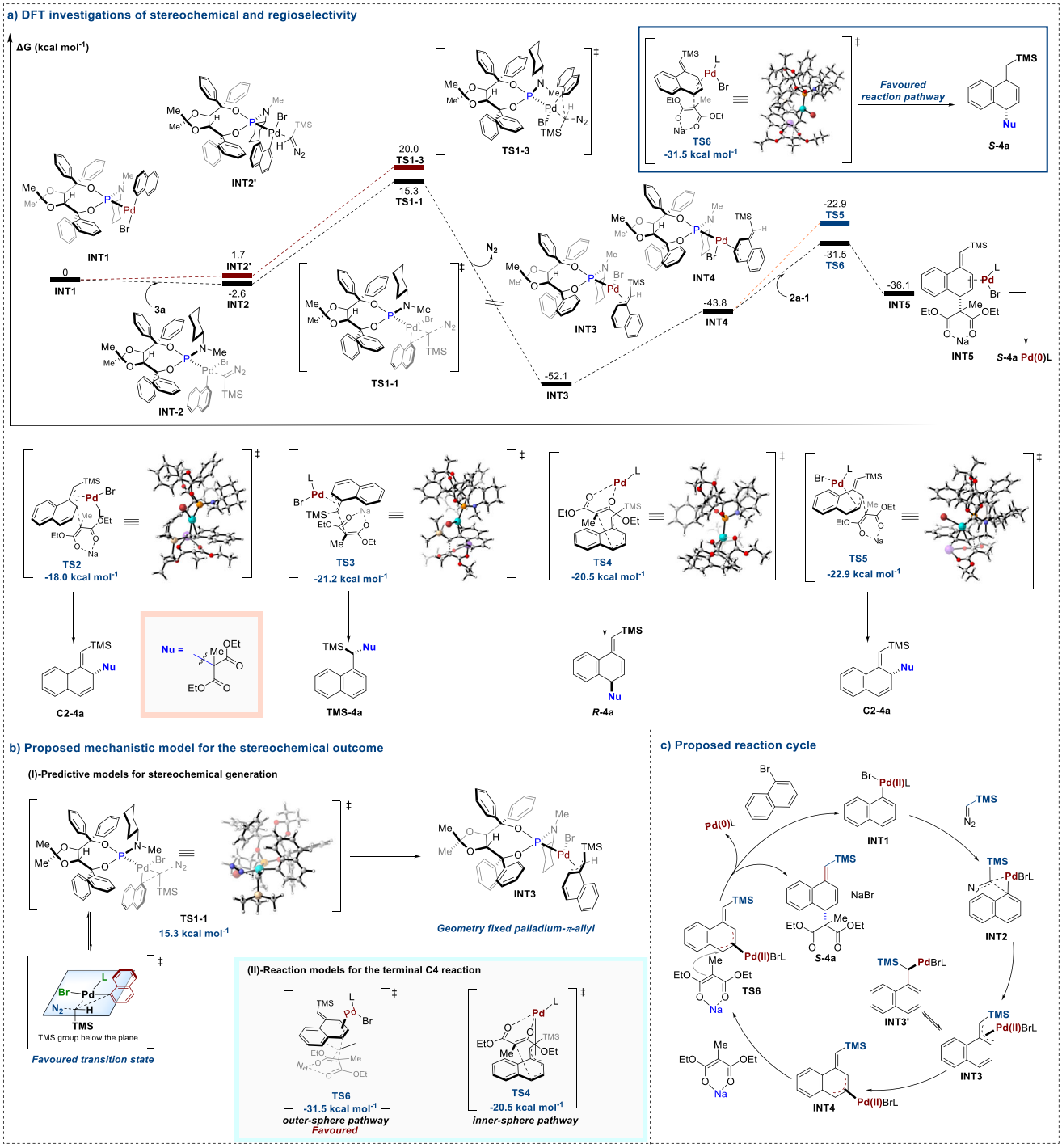

Figure 5. Mechanism investigations via DFT calculations. a) DFT investigations of the while productive pathway and alternative pathways for malonate attack. b) Stereochemical models for aryl insertion of a bound diazo compound with concomitant extrusion of N_2 and terminal C4 regioselectivity of malonate attack. c) Proposed reaction cycle.

the energy profile of the terminal C─C bond-forming step (Figure S18). Thus, the combined steric and electronic factors thus allow a highly selective outer-sphere allylic alkylation of sodium malonate, efficiently delivering the major isomer (*S*)-**4a**.

The computations reveal that the stereochemical outcome of the dearomatizative domino reaction is controlled by two stereodetermining events: (i) a ligand-controlled, enantioselective aryl insertion with N_2 extrusion that forms a chiral benzyl Pd complex, and (ii) subsequent terminal C4-regioselective outer-sphere allylic substitution that is regioselective and enantiospecific in the second C─C bond formation (Figure 5b). Based on our detailed DFT calculations of several possible mechanisms,[109–113] we propose

a catalytic cycle outlined in Figure 5c. The transformation commences with oxidative addition of 1-naphthyl bromide, generating key aryl palladium species **INT1**. This intermediate binds stereospecifically the diazo compound, and aryl α-insertion and concomitant extrusion of N_2, yielding intermediate **INT2** with chirality transfer from the chiral ligand. The resulting Pd-π-allylic complex **INT3** undergoes facile isomerization to internal π-allyl complex **INT4** while maintaining the oxocyclic *E*-silyl alkene. Steric interactions imposed by the C2 substituent govern the diastereoselectivity of this process, accounting for the observed *E*/*Z* mixture in product **4p** (Figure 3a). Subsequent outer-sphere nucleophilic attack by sodium malonate occurs exclusively at the C4 position, from the face opposite to palladium to form **TS6**. This stereospecific palladium (II)-mediated asymmetric allylic alkylation culminates in the formation of product (*R*)-**4a** and the active Pd catalyst.[114–118] The synergistic interplay between the chiral ligand environment, substrate steric and the noncovalent interactions with the π-unit accounts for the observed high levels of stereoselectivity throughout this cascade process.

Conclusion

In conclusion, we report here the first asymmetric three-component coupling of 1-bromonaphthalene, $TMSCHN_2$ and malonates. This cascade transformation exhibited good to excellent regio-, diastereo-, and enantioselectivities, enabled by a palldium catalyst of a new *monodentate phosphoramdite* **L10**. The products can be readily converted into 1,4-disubstituted hydrogenated naphthalenes, which are motifs of many bioactive terpenoids. Thus, we have applied the new catalytic reactions in synthesis of several bioactive terpenoids, including a short synthesis of (+)-erogorgiaene and a divergent synthesis of (−)-7-hydroxy-3,4-dihydrocadalin and (−)-odongrossin C from a common intermediate. DFT calculations reveal the origin of the enantiotropic formation of a chiral η^3-benzylic complex of palladium during aryl α-insertion of a diazo compound and the origin of terminal selectivity in the final malonate attack of the η^3-allylic complex. Future work will be devoted to other enantioselective dearomative transformations utilizing other types of η^3-benzylic intermediates.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Catalytic asymmetric dearomatization · Diazo compound · Difunctionalization · Palladium catalysis · Terpenoids

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