α-*N*-Phthalimido-Oxy Isobutyrate-Mediated Deoxygenative Arylation: Total Synthesis of Alanenses A and B

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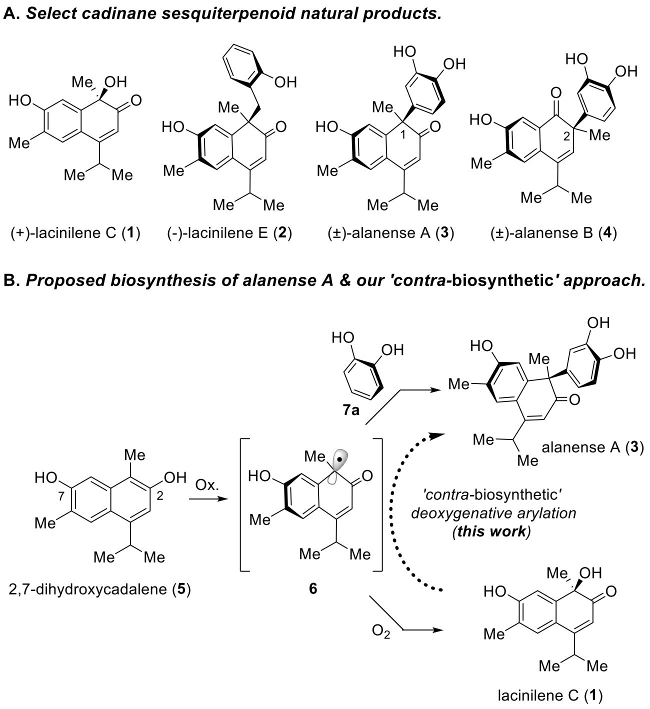
ABSTRACT: Inspired by our biosynthetic hypothesis for alanense A, we developed two distinct methods for the deoxygenative arylation of α-*N*-phthalimido-oxy isobutyrate (NPIB), derived from hydroxyl groups adjacent to or conjugated with a carbonyl moiety. One approach utilizes photoredox catalysis to achieve a radical-mediated arylation reaction. Alternatively, we designed an acid-mediated arylation method that proceeds through a cationic intermediate. The acid-mediated approach was successfully applied to the total syntheses of alanenses A and B, as well as O7′-methyllacinilene E.

Two-phase biosynthesis of terpene natural products, encompassing a cyclization phase followed by an oxidation phase, is a well-established process. Cadinane sesquiterpenoids conform to this paradigm. The cadinane framework, biosynthesized via the cyclization of farnesyl pyrophosphate, undergoes biosynthetic oxidations, resulting in remarkable structural diversity.[1,2] Lacinilene C (**1**), isolated from the cotton plant *Gossypium hirsutum* L., is an example of a highly oxidized cadinane sesquiterpenoid.[3] Notably, in 2018, lacinilene E (**2**), the benzyl substituted derivative of lacinilene C (**1**) was isolated.[4] More recently, alanenses A (**3**) and B (**4**), C1- and C2-arylated cadinane sesquiterpenoids were isolated as racemates from the leaves of *Alangium chinense* (Scheme 1A).[5] Importantly, alanenses A and B inhibit spontaneous calcium channel oscillations (SCOs) at low micromolar concentration. Initial structure-activity relationship studies revealed that the aromatic group at C1- and C2-position of alanense natural products is essential for the observed inhibitory activity toward SCOs.[5]

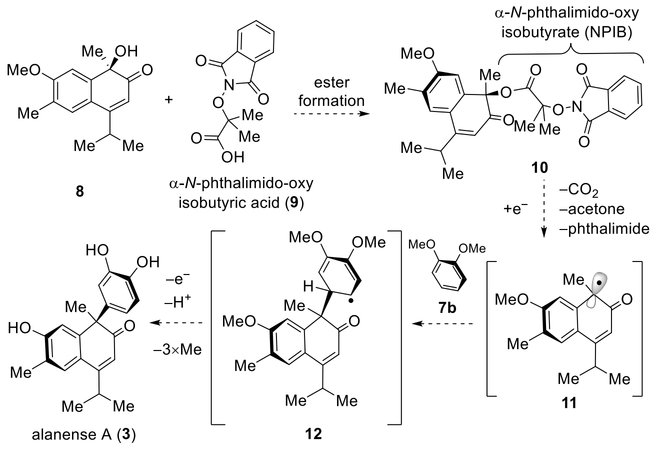
We hypothesized that alanense A (**3**) and lacinilene C (**1**) share a common biosynthetic precursor, namely 2,7-dihydroxycadalene (**5**). Previous studies have shown that 2,7-dihydroxycadalene undergoes air oxidation to form lacinilene C (**1**).[6] We proposed that this oxidation involves the reaction of a radical intermediate (**6**) with triplet oxygen. For the biosynthesis of alanense A (**3**), we speculated that the same radical intermediate (**6**) might instead react with catechol (**7a**). While the biosynthetic pathways of alanense A (**3**) and lacinilene C (**1**) diverge from the radical intermediate **6**, we questioned whether it might be possible to chemically revert lacinilene C (**1**) back to alanense A (**3**). Inspired by recent advancements in deoxygenative functionalization via radical intermediates,[7,8] we envisioned accessing alanense A (**3**) through a deoxygenative arylation[9–13] of lacinilene C (**1**) or its derivative in a "*contra*-biosynthetic" manner (Scheme 1B).[14]


A. ***Select cadinane sesquiterpenoid natural products.***

B. ***Proposed biosynthesis of alanense A & our 'contra-biosynthetic' approach.***

Scheme 1. Our synthetic blueprint towards alanense natural products.

We recently reported a radical-mediated deoxygenative transformation of tertiary alcohol derivatives to nitriles.[15] The key to success was the development of α-*N*-phthalimido-oxy isobutyrate (NPIB) as a novel redox-active handle for alcohols.[15] We envisioned utilizing NPIB moiety for the deoxygenative arylation of lacinilene C derivative as described in Scheme 2. Specifically, we planned to install the NPIB group to the tertiary alcohol moiety of lacinilene C 7-methyl ether (**8**). Single-electron transfer (SET) to the NPIB derivative **10** would result in α-carbonyl radical intermediate **11** upon release of phthalimide, carbon dioxide, and acetone (Scheme 2). Radical intermediate **11** was designed to react with catechol derivative **7b** to yield C–C coupled intermediate **12**. SET (oxidation), deprotonation, and subsequent demethylations of radical intermediate **12** would afford alanense A (**3**).



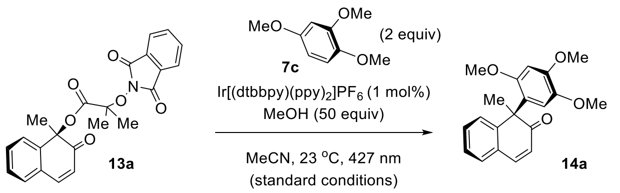
Scheme 2. Our initial synthetic design toward alanense A.

Our initial investigations focused on the deoxygenative arylation of NPIB derivative **13a** using $[Ir(dtbbpy)(ppy)_2]PF_6$ as a photoredox catalyst and methanol as a hydrogen bonding-mediated activator of the NPIB moiety.[16] To our delight, when NPIB derivative **13a** was allowed to react with 1,2,4-trimethoxybenzene (**7c**) in the presence of $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%) and methanol (50 equiv) upon 427 nm kessil lamp irradiation in acetonitrile, arylated product **14a** was isolated in 71% yield (Scheme 3A, entry 1). Notably, when the reaction was conducted without methanol, the product yield was significantly reduced (28%), highlighting the importance of hydrogen bonding-mediated activation of the NPIB moiety (Scheme 3A, entry 2).[16] On the same token, when the reaction was conducted in dimethylformamide (DMF), a strong hydrogen bonding acceptor, product **14a** was obtained in 32% yield consistent with diminished hydrogen bonding activation of the NPIB moiety (Scheme 3A, entry 3). In the absence of light, the reaction was not operative (Scheme 3A, entry 4). Markedly, the addition of BHT to the reaction mixture completely shut down the arylated product formation and resulted in **15** (81% yield) and **16** (40% yield based on the equivalence of NPIB derivative **13a**), consistent with the intermediacy of the radical intermediate (Scheme 3A, entry 5).

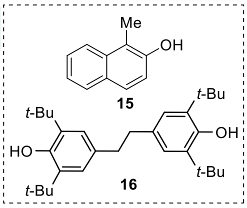
With the standard conditions established, the substrate scope for the photocatalytic deoxygenative arylation was investigated (Scheme 3B). Notably, acid- and/or base-sensitive functional groups such as Boc (**14b**), MOM (**14d**), Bn (**14e**), and silyl (**14f** and **14g**) were compatible with the reaction conditions. The substrate with the NPIB moiety juxtaposed between two carbonyl groups also produced the arylated product **14j** in 41% yield. The phenol derivative could also be employed as a coupling partner albeit with lower efficiency (**14i**, 36% yield). In this case, the phenol moiety's lower O–H bond dissociation energy enabled a hydrogen atom transfer to the radical intermediate producing **15** in 15% yield along with the oxidative dimer of the phenol derivative.

Based on our experimental and DFT-calculation results as well as related previous studies,[15,16] we proposed the catalytic cycle depicted in Scheme 3C. Photoexcited $[Ir^{III}]^*$ ($E_{1/2\ (IV/III^*)}$ = −0.96 V vs SCE) species would engage in hydrogen-bond assisted SET with **13a** to produce radical anion **A** which undergo highly facile fragmentation ($\Delta G^‡$ = 4.4 kcal/mol) to deliver electrophilic radical species **B**. The formation of the radical intermediate **B** was calculated to be a thermodynamically favorable process (–86.4 kcal/mol), and the subsequent radical addition to **C** is also smooth ($\Delta G^‡$ = 27.1 kcal/mol). The photoredox cycle is then completed by SET between **D** and the oxidizing $[Ir^{IV}]$ species leading to the formation of a cation, which undergoes aromatization to furnish **14a**.

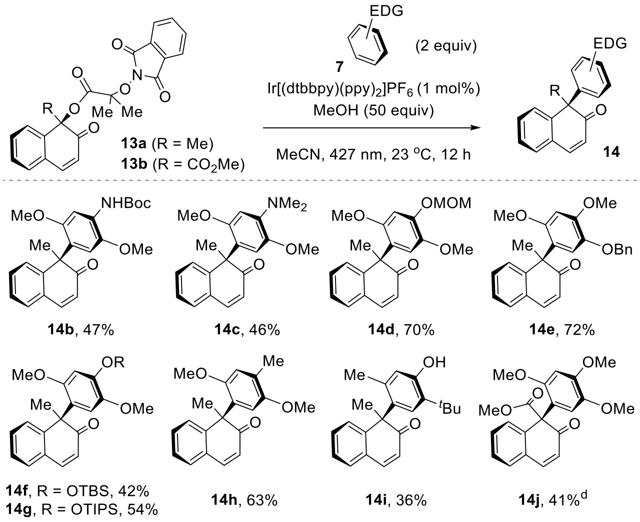
A. Development of a photocatalytic deoxygenative arylation with NPIB derivative.



entry	deviation from the standard conditions[a]	yield (%)[b]
1	none	79 (71[c])
2	w/o MeOH	28
3	DMF instead of MeCN	32
4	w/o 427 nm irradiation	no reaction
5	BHT (2 equiv)	0



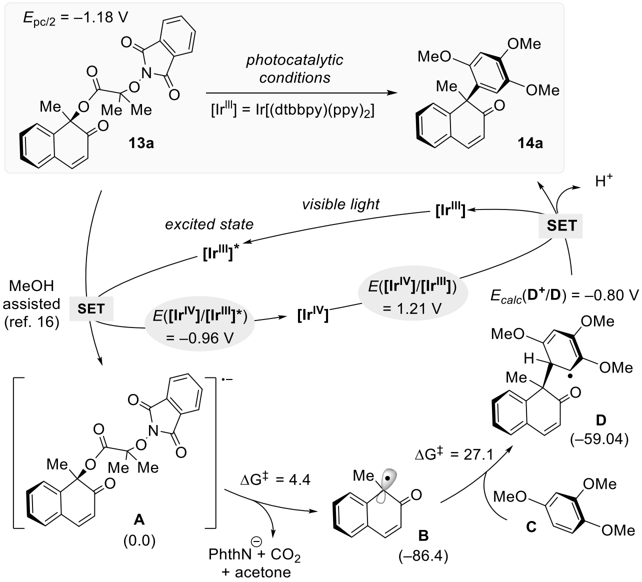
B. Substrate scope of the photocatalytic deoxygenative arylation.[a,c]



14b, 47% **14c**, 46% **14d**, 70% **14e**, 72%

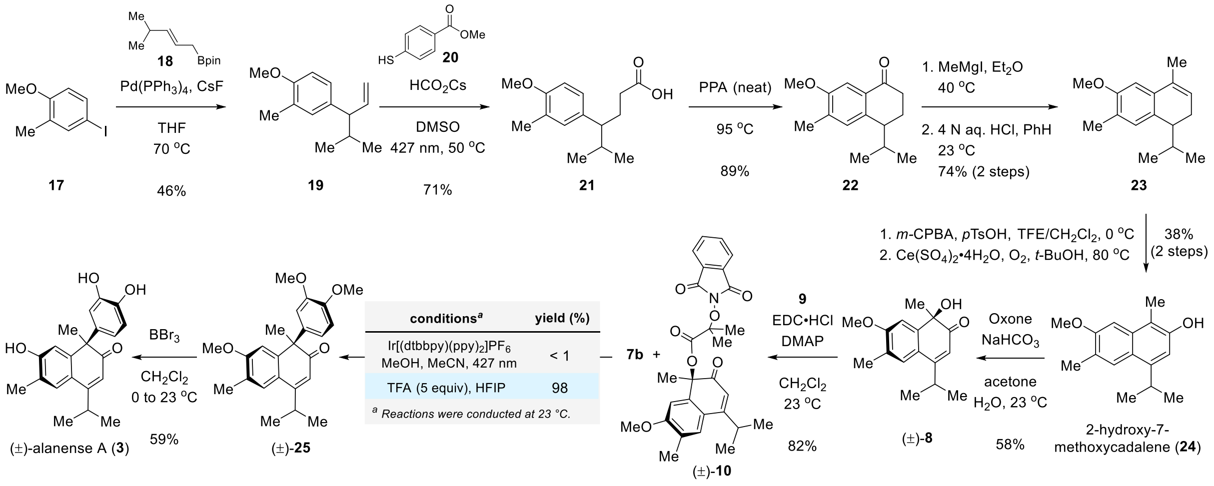
14f, R = OTBS, 42%
14g, R = OTIPS, 54% **14h**, 63% **14i**, 36% **14j**, 41%[d]

C. Proposed catalytic cycle.[e]



Scheme 3. Development of NPIB-mediated photocatalytic deoxygenative arylation. [a]All reactions were carried out on 0.1 mmol scale (**13a** and **13b**) and at 0.2 M. [b]Yield was determined by the NMR analysis of the crude reaction mixture using dibromomethane as internal standard. [c]Isolated yield. [d]**14j** was synthesized from **13b**. [e]Reduction potentials were noted in V vs SCE (standard calomel electrode). Computation level = M06-2X/6-311+G** (SMD, solvent=acetonitrile) | M06-2X/6-31G** (SMD, solvent=acetonitrile); Unit = kcal/mol.

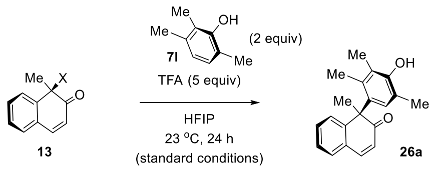
After developing the NPIB-mediated photocatalytic deoxygenative arylation, we turned our attention to its application in the total synthesis of alanense natural products.[17,18] Our synthesis commenced with a regioselective reverse-prenylation of commercially available **17** using prenylboronic ester **18**[19] in the presence of $Pd(PPh_3)_4$ and CsF[20] to afford coupled product **19** in 46% yield (Scheme 4). With terminal alkene **19** in hand, we then employed Wickens' radical hydrocarboxylation to produce homologated carboxylic acid **21** in 71% yield.[21] Subsequently, carboxylic acid **21** was transformed to cadinane framework **23** based on McCormick's protocol.[22] Epoxidation of compound **23** followed by an oxidative epoxide opening reaction afforded natural 2-hydroxy-7-methoxycadalene (**24**) in 38% yield.[23] Oxone-mediated dearomatization of naphthol derivative **24** yielded α-hydroxyketone **8** in 58% yield.[24] Esterification of the tertiary alcohol group in compound **8** with α-*N*-phthalimido-oxy isobutyric acid (**9**) was achieved in 82% yield in the presence EDC·HCl and DMAP. With NPIB derivative **10** in hand, the stage was set for the deoxygenative arylation reaction. However, an intractable mixture of products was observed when NPIB derivative **10** and 1,2-dimethoxybenzene (**7b**) were subjected to the aforementioned standard photoredox catalytic conditions (Scheme 4). We speculate that the increased electron density of the α-keto radical intermediate and the decreased electron density of the aromatic coupling partner caused a polarity mismatch during the key C–C bond formation. In fact, DFT-calculation revealed that the activation barrier for the C–C coupling between radical intermediate **B** (Scheme 3C) and 1,2,4-trimethoxybenzene is 27.1 kcal/mol, while the activation energy for the coupling between radical **11** and 1,2-dimethoxybenzene is 32.4 kcal/mol (for details, see the Figure S4). Extensive experimentations were conducted with a model system to remedy the observed lack of desired reactivity under our previously optimized photocatalytic reaction conditions. To our delight, we discovered that NPIB derivative **10** and 1,2-dimethoxybenzene (**7b**) could be coupled in the presence of 5 equiv of TFA in hexafluoroisopropanol (HFIP) to yield product **25** in 98% yield (*vide infra*). It is noteworthy that the carbocationic moiety is efficiently formed at the α-position of the ketone from the NPIB group under our newly discovered optimized reaction conditions. Treatment of trimethylated compound **25** with 10 equiv of BBr_3 afforded the synthetic sample of alanense A (**3**) in 59% yield.



Scheme 4. Total synthesis of alanense A.

The optimization studies toward the key NPIB-mediated Friedel–Crafts-type arylation are shown in Table 1. Treatment of NPIB derivative **13a** and 2,3,6-trimethylphenol (**7l**, 2 equiv) with TFA (5 equiv) in HFIP solution produced deoxygenative arylated product **26a** in 80% isolation yield along with α-*N*-phthalimido-oxy isobutyric acid (**9**, Table 1, entry 1). The use of HFIP as a solvent was critical as the reaction did not proceed when acetonitrile, DMF, tetrahydrofuran, methylene chloride, or methanol were employed as a solvent (Table 1, entries 2–6).[25,26] TFA was the optimal acid for the reaction since other Brønsted acids such as formic acid or acetic acid resulted in full recovery of NPIB derivative **13a** (Table 1, entries 7 and 8). When stronger triflic acid was employed, NPIB derivative **13a** underwent undesired decomposition leading to only 4% of coupled product **26a** (Table 1, entry 9). In the absence of TFA, the reaction did not proceed at all (Table 1, entry 10). The use of 1 or 3 equiv of TFA resulted in lower product yields due to slower conversion (Table 1, entries 11 and 12). The reaction proceeded in the dark, indicating that the mechanism does not involve a photoinduced radical pathway (Table 1, entry 13).

Next, the reactivity of the NPIB group was compared with other leaving groups. When hydroxyl derivative **13c** was employed as a substrate under the optimized reaction conditions, the desired arylated product **26a** was obtained in 22% yield (Table 1, entry 14).[27,28] Other carboxylate-based leaving groups such as acetate (**13d**), pivalate (**13e**), benzoate (**13f**), and methyl oxalate (**13g**) exhibited lower yields compared to the NPIB group (Table 1, entries 15–18). Notably, the dissociation of NPIB following protonation was calculated to be thermodynamically favorable (ΔG = –5.3 kcal/mol), whereas the analogous processes involving the alcohol and acetate substrates were slightly endergonic (ΔG = +9.1 and +3.1 kcal/mol, respectively), indicating the superior leaving group ability of NPIB (for details, see the Figure S6). Even though the product yields were lower, the formation of the coupled product **26a** with these leaving groups suggests the intermediacy of a carbocation species. Subjection of bromide derivative **13h** under the optimized reaction conditions did not yield the desired coupled product (Table 1, entry 19) and only reduced product **15** and 4-bromo-2,3,6-trimethylphenol were observed.

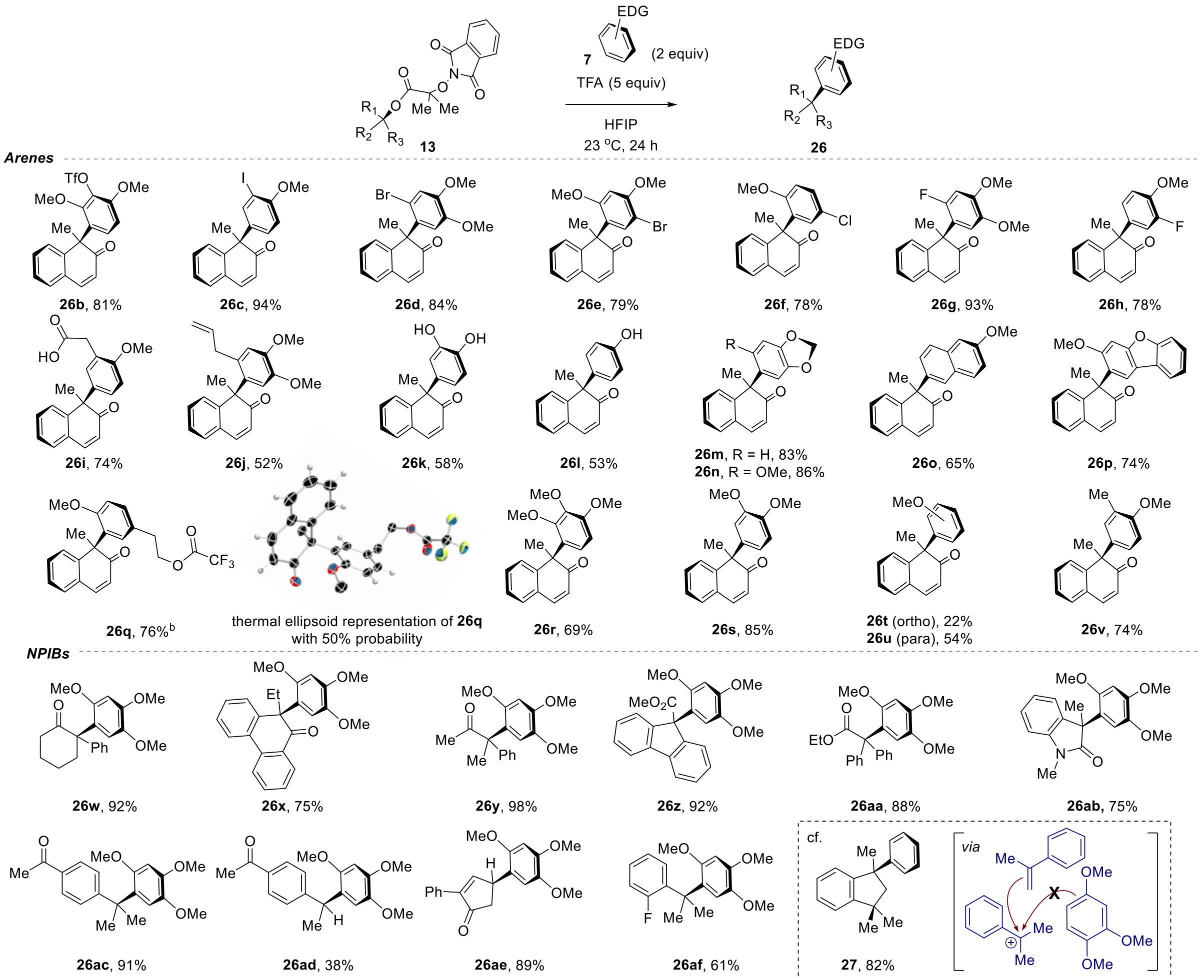


entry	substrate	deviation from the standard conditions[a]	yield (%)[b]
1	**13a** (X = NPIB)	none	84 (80[c])
2	**13a**	MeCN instead of HFIP	no reaction
3	**13a**	DMF instead of HFIP	no reaction
4	**13a**	THF instead of HFIP	no reaction
5	**13a**	CH_2Cl_2 instead of HFIP	no reaction
6	**13a**	MeOH instead of HFIP	no reaction
7	**13a**	HCOOH instead of TFA	no reaction
8	**13a**	AcOH instead of TFA	no reaction
9	**13a**	TfOH instead of TFA	4
10	**13a**	TFA (0 equiv)	no reaction
11	**13a**	TFA (1 equiv)	43
12	**13a**	TFA (3 equiv)	74
13	**13a**	in the dark	82
14	**13c** (X = OH)	none	22
15	**13d** (X = OAc)	none	26
16	**13e** (X = OPiv)	none	4
17	**13f** (X = OBz)	none	12
18	**13g** (X = $O(CO)_2OMe$)	none	13
19	**13h** (X = Br)	none	0

Table 1. Optimization of the acid-mediated deoxygenative arylation. [a]All reactions were carried out on 0.1 mmol scale (**13a** and **13c**–**13h**) and at 0.25 M. [b]Yield was determined by the NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield.

The substrate scope of aryl coupling partners was consequently investigated (Table 2). Triflate (**26b**), iodide (**26c**), bromide (**26d** and **26e**), chloride (**26f**), and fluoride (**26g** and **26h**) groups were compatible with our newly discovered reaction conditions. It is noteworthy that the presence of inductively electron-withdrawing halides did not hamper the reaction outcomes. The carboxylic acid and the terminal olefin groups were compatible under the standard reaction conditions (**26i** and **26j**). The phenolic moiety, which was problematic under the previously described photocatalytic reaction conditions, was compatible under the optimized TFA+HFIP reaction conditions (**26k** and **26l**). Bicyclic (**26m**–**26o**) and tricyclic (**26p**) aromatic systems yielded the coupled products in good yields. The substrate with a primary hydroxyl group could be employed in our coupling reaction conditions. In this case, the hydroxyl group underwent trifluoroacetylation (**26q**). Notably, when anisole was employed as a coupling partner, *ortho*- and *para*-regioisomers were obtained in 22% and 54% isolation yields, respectively. It is noteworthy that for all other cases delineated here, products were obtained as a single regioisomer.

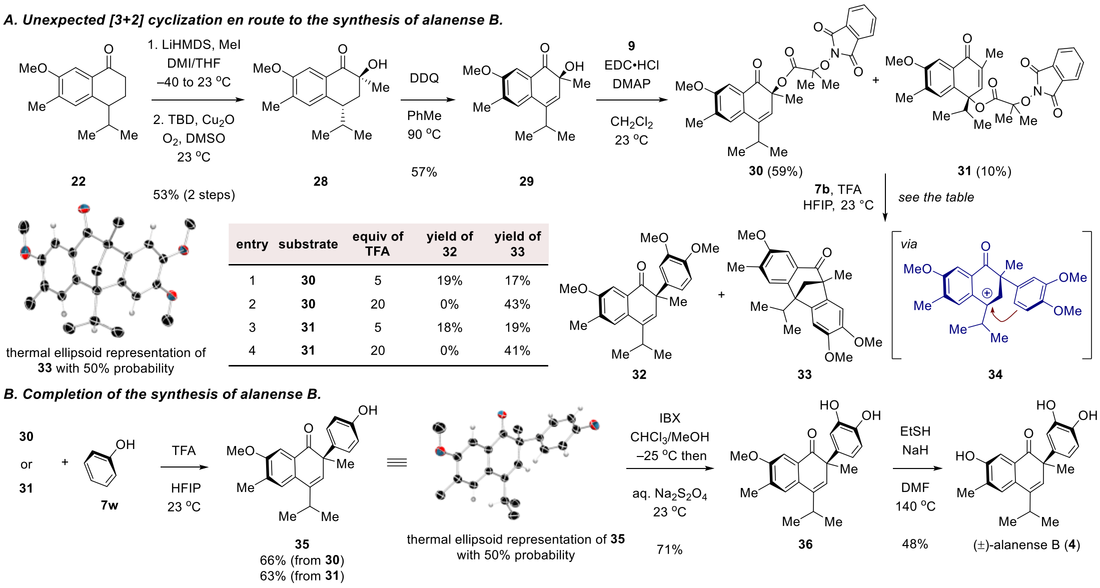
Table 2. Substrate scope of the NPIB-mediated arylation reaction.[a]



[a]All reactions were carried out on 0.1 mmol scale (**13a** and **13i**–**13s**) and at 0.25 M. [b]TFA (20 equiv) was used.

We subsequently surveyed the scope of NPIB derivatives. Structurally diverse benzylic and tertiary NPIB derivatives yielded coupling products with 1,2,4-trimethoxybenzene in good yields. The presence of an ester (**26z** and **26aa**) or an amide moiety (**26ab**) at the α-position of the NPIB did not hinder the reaction. As long as the ketone group is conjugated to the carbon attached to the NPIB group either via an aromatic ring (**26ac** and **26ad**) or an olefin (**26ae**), the arylated products were formed in moderate to good yield. Notably, secondary NPIB derivatives were successfully transformed into arylated products under the standard reaction conditions (**26ad** and **26ae**). Interestingly, when the NPIB derivative of 2-phenylpropan-2-ol was subjected to the standard reaction conditions, homodimerization product **27** was formed in 82% yield. It is reasoned that the benzylic carbocationic intermediate is trapped with *in-situ* generated α-methylstyrene. When the analogous NPIB derivative with an *ortho*-fluoride moiety at the phenyl group was employed, the desired arylated product (**26af**) was obtained in 61% yield.

We next embarked on the total synthesis of alanense B (**4**). α-Methylation of common ketone precursor **22** and subsequent α-hydroxylation of the resulting methylated product via a protocol reported by the Schoenebeck group[29] resulted in alcohol **28** in 53% yield over two steps (Scheme 5). Oxidation of compound **28** with DDQ produced conjugated alcohol **29** in 57% yield. Treatment of alcohol **29** with NPIB acid **9** in the presence of EDC·HCl and DMAP forged NPIB derivative **30** as a single regioisomer. However, NPIB derivative **30** was partially isomerized to **31** during silica gel column chromatography to yield **30** and **31** in 59% and 10% yield, respectively. Interestingly, treatment of **30** with 1,2-dimethoxybenzene (**7b**) and 5 equiv of TFA in HFIP solution yielded desired arylated product **32** (19%) along with [3+2] cycloaddition product **33** (17%), likely formed via cationic intermediate **34**. When **30** was allowed to react with 20 equiv of TFA in HFIP, only cycloaddition product **33** was obtained in 43% yield. The structure of [3+2] cycloaddition product **33** was unambiguously confirmed by a single crystal X-ray diffraction analysis.[30] It is notable that the bicyclo[3.2.1]octadienone framework in **33** constitutes the backbone of various natural products including naphthocyclinone.[31] The subjection of the NPIB regioisomer **31** to these reaction conditions revealed analogous reaction outcomes.



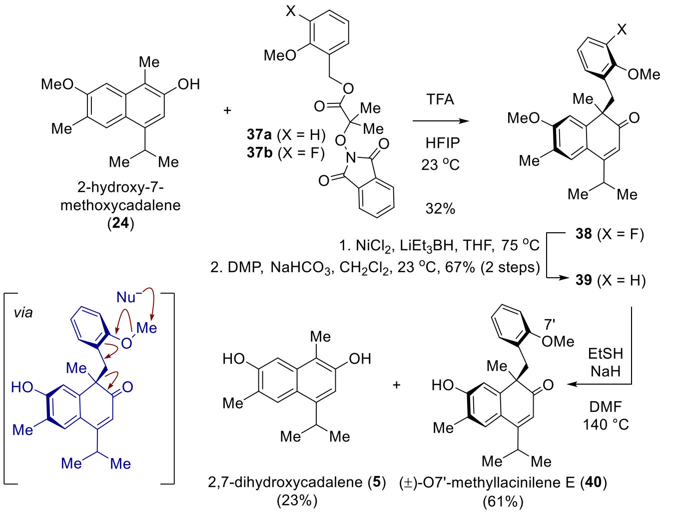
entry	substrate	equiv of TFA	yield of 32	yield of 33
1	**30**	5	19%	17%
2	**30**	20	0%	43%
3	**31**	5	18%	19%
4	**31**	20	0%	41%

Scheme 5. Total synthesis of alanense B.

To circumvent the formation of the [3+2] cycloaddition byproduct, phenol (**7w**) was selected as the coupling partner. We reasoned that the undesired intramolecular Friedel–Crafts reaction-based cyclization would not be feasible because the *meta* position of phenol group is deactivated by an inductively electron-withdrawing oxygen atom. This strategic design was possible owing to the broad substrate scope of the newly developed TFA/HFIP-based arylation. In the event, when NPIB derivative **30** (or **31**) was allowed to react with phenol in the presence of TFA (5 equiv) in HFIP, the desired α-arylated product **35** was exclusively formed in 66% yield (63% yield from **31**). The exclusive arylation at the α-position of the ketone group is noteworthy. Based on DFT calculations, nucleophilic phenol addition at the α-position is kinetically favored ($\Delta G^\ddagger$ = 14.5 kcal/mol) over addition at the benzylic position ($\Delta G^\ddagger$ = 17.2 kcal/mol), presumably due to the significant steric hindrance posed by the benzylic isopropyl substituent (for details, see the Figure S7).

For the endgame of the synthesis, phenol derivative **35** was oxidized to the orthoquinone derivative in the presence of IBX at –25 ℃. Subsequent one-pot addition of aqueous sodium dithionite solution to the reaction mixture resulted in catechol derivative **36** in 71% yield. The use of chloroform/methanol co-solvent was critical for the efficient transformation.[32] The final demethylation of the methoxy group in **36** was achieved by treating it with ethanethiol and sodium hydride in DMF to produce the first synthetic sample of alanense B (**4**) in 48% yield.

Finally, we envisioned applying the newly developed NPIB-based deoxygenative transformation into the synthesis of lacinilene E (**2**, Scheme 6). To this end, 2-hydroxy-7-methoxycadalene (**24**) was allowed to react with NPIB derivative **37a** in the presence of TFA in HFIP. However, only the decomposition of NPIB derivative **37a** was observed under these reaction conditions. We speculated that the electron-rich NPIB derivative **37a** acts as a dominant nucleophile over 2-hydroxy-7-methoxycadalene (**24**). To temper the nucleophilic reactivity of the NPIB derivative, we designed fluorinated NPIB derivative **37b**. To our delight, when **24** was allowed to react with fluorinated NPIB derivative **37b** in the presence of TFA in HFIP, the coupled product **38** was formed in 32% yield. $NiCl_2$-catalyzed hydrodefluorination using superhydride as a reductant[33] afforded the defluorinated allylic alcohol product from compound **38**. Subsequent DMP-mediated oxidation of the resulting alcohol resulted in dimethylated lacinilene E derivative **39** (67% yield over two steps). Demethylation at O7′ position was extremely challenging. 2,7-dihydroxycadalene (**5**) was obtained as a major product in various demethylation conditions attempted. We reasoned that the demethylation at O7′ induced the C–C bond cleavage via the formation of an *ortho*-quinone methide. In fact, when compound **39** was reacted with boron tribromide as a demethylating agent, a trace amount of lacinilene E (**2**) was obtained along with 2,7-dihydroxycadalene as a major product (for details, see the Figure S1). Subjection of compound **39** to ethanethiol and sodium hydride in DMF delivered the methylated congener O7′-methyllacinilene E (**40**) in 61% yield along with 2,7-dihydroxycadalene (**5**) in 23% yield.



Scheme 6. Synthesis of the core of lacinilene E.

In conclusion, we have completed the total synthesis of alanenses A and B. To achieve the biosynthetically-inspired[34,35] arylation, we designed deoxygenative arylation reactions of α-hydroxycarbonyl derivatives. By utilizing α-*N*-phthalimido-oxy isobutyrate (NPIB) as a redox-active handle for hydroxyl groups, we have established a photoredox-catalyzed deoxygenative arylation reaction that proceeds via radical intermediates. Although challenges arose when applying this photocatalytic approach to the synthesis of alanense A, we overcame these obstacles by developing an alternative method using TFA/HFIP, which enabled the arylation of the NPIB derivative *en route* to the natural product. Notably, our work demonstrated that the combination of the NPIB group with TFA and HFIP effectively promotes Friedel–Crafts reactions, even in the challenging context of generating carbocations adjacent (or conjugated) to electron-withdrawing groups such as carbonyl moieties. This methodology enabled streamlined total syntheses of alanenses A and B, and O7′-methyllacinilene E. Ongoing studies aim to further explore and expand the versatile reactivity of the NPIB group, with findings to be presented in future reports.

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