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New Approach to 4-Phenyl-β-aminotetralin from 4-(3-Halophenyl) tetralen-2-ol Phenylacetate

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Abstract

Mixed trifluoroacetyl phenylacetyl anhydride and 3-halostyrenes (fluoro, chloro, and bromo) or vinylcycloalkanes (cyclohexyl, cyclooctyl), undergo cascade Friedel-Crafts cycli-acylalkylation, enolization, and *O*-acylation to give 4-substituted tetralen-2-ol phenylacetates, without additional solvent in good yields. Base alcoholysis of 4-phenyltetralen-2-ol phenylacetate reveals the tetral-2-one for asymmetric transfer hydrogenation. Bromophenyltetralen-2-ol phenylacetate undergoes Suzuki coupling, and provides a short route to *trans*-4-phenyl-β-aminotetralin.

Keywords

β-aminotetralin; cascade; halostryene; phenylacetate; tetralen-2-ol

The β-aminotetralin moiety is a pharmacophore element recognized by several classes of aminergic neurotransmitter G protein-coupled receptors (GPCRs). For example, asymmetric (–)-*trans*-4*R*-phenyl-2*S*-dimethylaminotetralin (**1**, Scheme 1) exhibits anorectic and antipsychotic efficacy after peripheral administration to rodents via actions at brain serotonin (5-hydroxytryptamine, 5-HT) 5-HT_2 GPCRs.[1] The 4-(3-halophenyl) analogs of **1**[2] are active at 5-HT_2 receptors, important drug targets for many human psychological and physiological disorders. Halophenyltetralen-2-ol phenylacetate **3** intermediates, from readily available reagents **4** and [**5**] (Scheme 1), provide these analogs and avoid the requirement to isolate corresponding 4-(3-halophenyl)tetral-2-ones **2**. Versatile aryl halide and enol phenylacetate functionalities on **3** make these molecules useful for diversified organic syntheses, pharmaceuticals, and catalyzed asymmetric transformations.[3]

Although 4-phenyltetral-2-ones are of great interest to organic synthesis, methods to synthesize them are low yielding, scarce, difficult to diversify, and require fast, efficient use to avoid decomposition.[4] Direct ring-closure reports to non-halogenated 4-phenyltetral-2-one **2a** include (Scheme 2): (a) dimethylamine addition to symmetrical dibenzoylethylene **6** gives 2-(*N*,*N*-dimethylamino)-1,4-diphenyl-1,4-butanedione, to reduce and then cyclize in refluxing

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Supporting Information Available

General experimental methods, procedures, characterization data, copies of ^{1}H and ^{13}C-NMR spectra for synthesized compounds. This material is available free of charge via the Internet at

acid;[5] (b) enolate addition of phenylacetone **7** to benzaldehyde provides 1,4-diphenylbut-1-en-3-one, to cyclize under Friedel-Crafts (FC) conditions with metal Lewis acid or PPA;[6] (c) one-step FC-cycli-acylalkylation (FC-CAA)7 with phenylacetyl chloride **8**, styrene **4a** (or TMS activated **4a**), and metal Lewis acid in dichloromethane.[8] Free of many aforementioned drawbacks one-step FC-CAA (d) with phenylacetic acid **9**, TFAA, phosphoric acid,[9] and **4a**, readily dimerizes **4a** and furnishes only a trace amount of **2a** by GC-MS.[10] While, mixed trifluoroacetyl phenylacetyl anhydride [**5**] can esterify alcohols[11] or FC-acylate aryls to give **10**, one report includes traces of aryl enolates **11**.[12] Stable tetralen-2-ol phenylacetates avoid difficulties handling and storing expensive 4-phenyltetral-2-ones and are made directly with one procedure, without additional solvent. We now report a facile cascade reaction to 4-(3-halophenyl)tetralen-2-ol phenylacetates and their utility in asymmetric transfer hydrogenation (ATH), palladium cross-coupling, and palladium hydrodebromination applications.

Cascade FC-CAA, enolization, and *O*-acylation was investigated with TFAA activated phenylacetic acid and **4a**, 3-halostyrenes **4b–d** (Table), as well as, vinylcycloalkanes **4e,f** (Scheme 3). Reactive **4a** was heated to 60 °C prior to reaction with [**5**] in order to accelerate the inherently slow enolization[13] of **2a** in the reaction media and allow isolation of *O*-acylated **3a** (15%). At rt, or cooling to −78 °C, resulted in loss of reactive **2a** in a complex mixture. Additional solvents (ACN, hexanes, dichloromethane) resulted in self-condensed phenylacetyl anhydride with styrene persisting, as did addition of **4a** to the activated acid. Surprisingly, moderately reactive 3-halostyrenes **4b–d**[14] withstood dimerization in the reaction media and resulted in higher conversions to the desirable tetral-2-one. Equimolar 3-fluorostyrene **4b** and [**5**] gave major **2b** (42%) and minor **3b** (8%). Chlorophenyltetral-2-one **2c** (70%) was prepared from 3-chlorostyrene **4c** with 3-equiv of [**5**], and underwent further treatment with equimolar [**5**] to provide **3c** (38%). Warming to rt over 24 h 3-bromostyrene **4d** with 3-equiv of [**5**] gave **3d** (50%), over 3-fold increase in yield from non-halogenated **3a**. Vinylcyclohexane **4e** and vinylcyclooctane **4f** provided solids **3e** (63%) and **3f** (40%), respectively, when reacted separately with [**5**]. Conformational difference between 4-cycloalkyltetralen-2-ol and 4-phenyltetralen-2-ol cores was indicated by allylic proton coupling in the former. Tetralen-2-ol phenylacetates were isolated with less than 5% of the regioisomer (unlike silyl tetralen-2-ol ethers15), stable to atm, and enantio-resolvable using chiral stationary phase (CSP)-HPLC (e.g., for **3e**, t_{R1} = 15.7 $[\alpha]^{25}{}_{D}$ = −79.1, t_{R2} = 16.8 $[\alpha]^{25}{}_{D}$ = +78.8.

Three steps (Scheme 4), (a) ATH,[16] (b) tosylation, and (c) S_N2 inversion with aq dimethylamine,[17] provided enantioenriched *cis*-(4*R*-2*R*)-**12a** (74%), *cis*-(4*R*-2*R*)-**13** (75%), and *trans*-(4*R*-2*S*)-**1** (70%) with β-hydride elimination byproducts.[18] Pure *trans*-4*R*-2*S*-**1** was obtained by CSP-HPLC (74% *ee*). Carbonyl reduction of **3d** with (d) sodium borohydride gave **12d** (90%) and (e) hydrodebromination[19] provided (±)-**12a** (99%). Employing brominated **3d** in one additional step gave (±)-**12a** in 45% yield from reagents, an improvement over the 11% yield using the non-halogenated **3a**. Suzuki coupling[20] of **3d** with (f) phenylboronic acid smoothly provided 4-(biphenyl-3-yl)tetralen-2-ol phenylacetate **14** (70%). Thus, simple palladium insertion modifications to bromophenyl functionality with **3d** and **12d** were established.

Cascade Friedel-Crafts cycli-acylalkylation, enolization, and *O*-acylation with activated phenylacetic acid and moderately reactive halostyrene or vinylcycloalkanes, provides 4-(3-halophenyl or cycloalkyl)tetralen-2-ol phenylacetate. An electron withdrawing substituted styrene dimerizes less and provides higher yields in the reaction media than unsubstituted styrene. Base alcoholysis on 4-phenyltetralen-2-ol phenylacetate reveals 4-phenyltetral-2-one for use *in situ*. Simple palladium insertion cross-coupling with 4-(3-bromophenyl)tetralen-2-ol phenyl-acetate is established and a short 5-step sequence provides a 3-times (6% to 18%) more efficient route to *trans*-**1**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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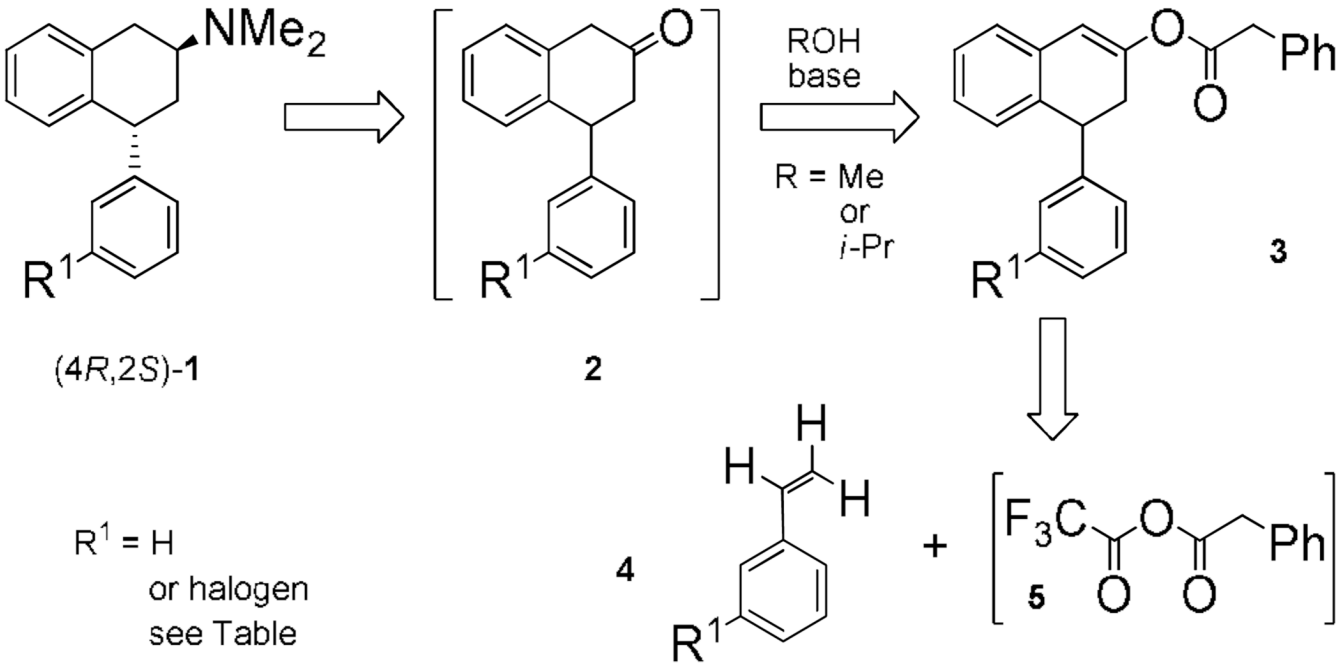
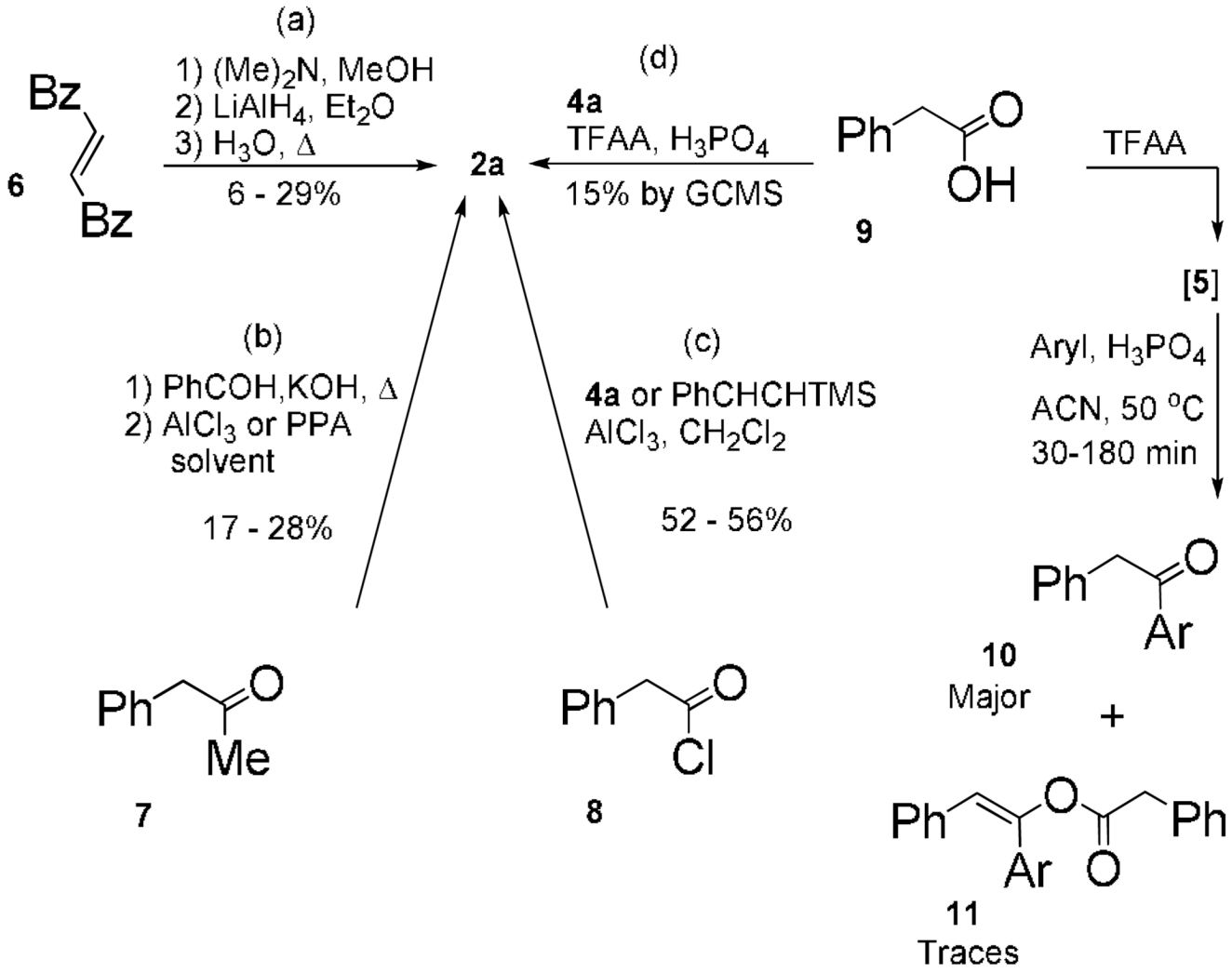
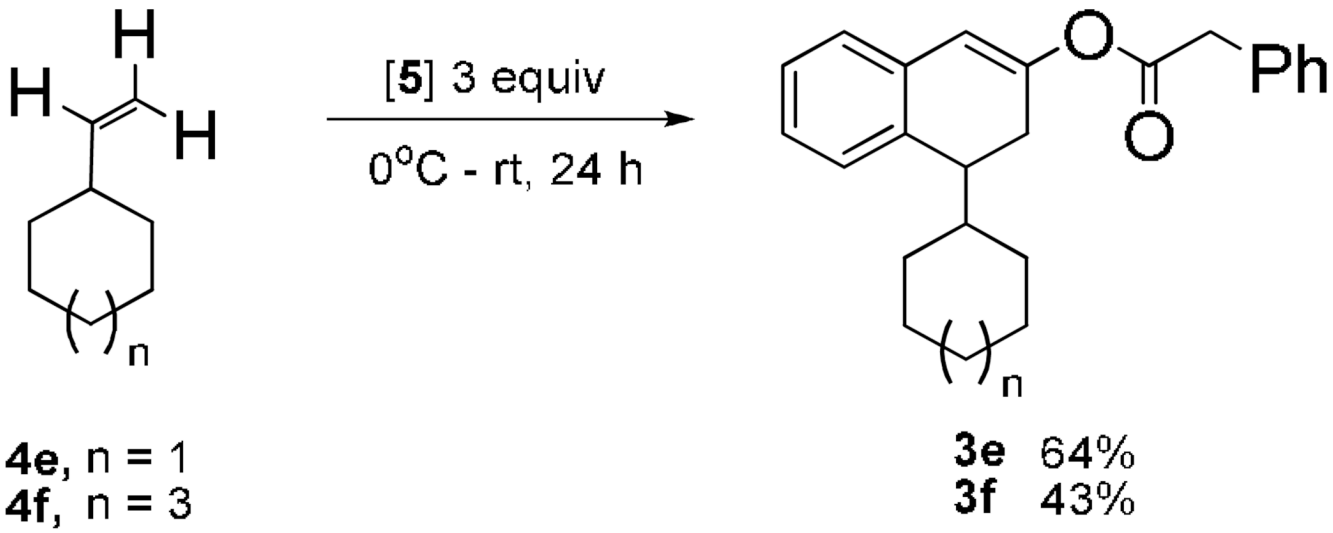


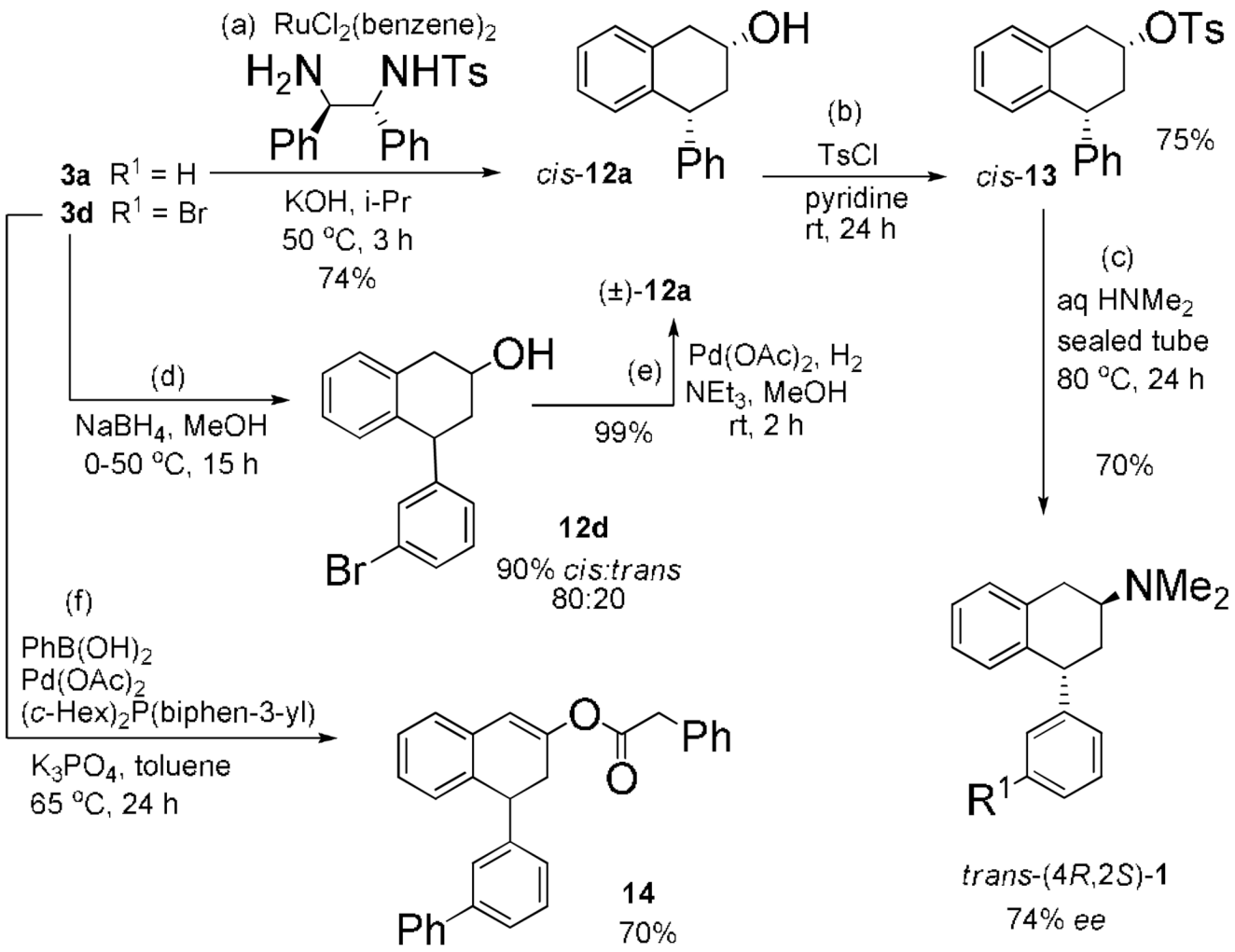
Scheme 1.
Retrosynthesis to *trans*-4-Phenyl-β-aminotetralins.



Scheme 2.
Literature Examples for 4-Phenyltetral-2-one.



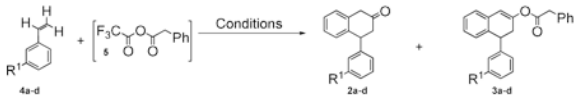
Scheme 3.
Cascade Reaction with Vinylcycloalkanes.



Scheme 4.
Utility of 4-(3-Bromophenyl)tetralen-2-ol Phenylacetate.

Table

Cascade Reaction with Styrene or 3-Halostyrenes for **2** and **3**, Conditions, Yields, and UV Trace.



		Yield (%)[a]		Conditions			UV[e] Trace of 3	
R[1]	**4**	**2**	**3**	**[5]:4[c]**	**temp (°C)**	***t* (h)**	t_{R1}	t_{R2}
H	**a**	0	15	3:1	0–60	0.5	17.7	18.1
F	**b**	42	8	1:1	0	0.5	16.0	16.8
Cl	**c**	70	0(38)[b]	3:1	0	0.5	17.9	18.9
Br	**d**	0	50	3:1	0–rt	24[d]	18.7	20.1

[a] isolated yield;

[b] from 2c;

[c] equiv;

[d] reaction time not minimized;

[e] 220/254 nm, CSP-HPLC.