

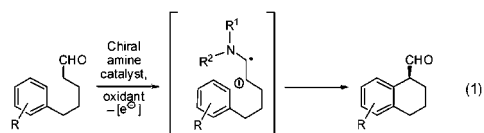
## Enantioselective Intramolecular Friedel–Crafts-Type $\alpha$ -Arylation of Aldehydes

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Enantioselective organo-SOMO catalysis has, in the last two years, been the subject of considerable development and exploration. A number of new and unique transformations have been reported, such as  $\alpha$ -allylation,<sup>1a</sup>  $\alpha$ -oxyamination,<sup>2</sup>  $\alpha$ -enolization,<sup>1b</sup> and  $\alpha$ -vinylation,<sup>3</sup> of aldehydes. Herein, we report a modification of this activation mode that involves the intramolecular Friedel–Crafts type  $\alpha$ -arylation of aldehydes<sup>4</sup> carrying electron-donating groups on their aromatic nucleus (eq 1) and its application to the total synthesis of demethyl calamenene (7, Scheme 2),<sup>5</sup> a potent cytotoxic agent against human adenocarcinoma A 549.



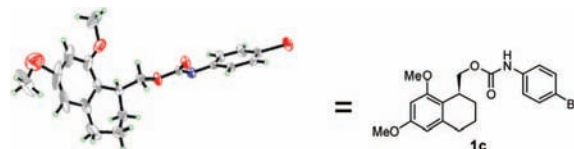
As a model reaction, we investigated the reactivity of aldehyde **1a**, a supreme substrate for Friedel–Crafts reaction in the presence of various secondary amines as catalysts and under different reaction conditions (Table 1). As oxidant, cerium(IV) ammonium nitrate (CAN) was employed, since its use as a suitable reagent for the oxidation of enamines has been demonstrated.<sup>6</sup> Proline-<sup>7</sup> and diphenylprolinol-based<sup>8</sup> ligands showed no catalytic activity under various reaction conditions and, in most cases, underwent oxidation and depletion. However, chiral 2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone ((*2R,5R*)-**A**) was proven to be effective as a catalyst for the reaction, both in terms of efficiency and enantioselectivity (entry 4, Table 1). Interestingly, the related 2,2,3-trimethyl-5-benzyl-4-imidazolidinone proved inefficient as a catalyst for this transformation. From screening various solvents, it was found that the polarity of the solvent had a significant effect on the outcome of the reaction (entries 1–5, Table 1). Thus, acetone and DME were proven to be superior as solvents. The use of other oxidants, such as  $K_3Fe(CN)_6$ ,  $(NH_4)_2S_2O_8$ ,  $Mn(OAc)_3$ , DDQ, and BAIB, resulted in decomposition of both substrate and catalyst. To further improve the reaction outcome, various additives were screened. It was found that water is of utmost importance for this process, as the reaction in DME under anhydrous conditions led to erosion of yield (entry 6, Table 1). Additionally, several basic cocatalysts showed no overall improvement (entries 7–10, Table 1).

The absolute configuration of the bicyclic aldehyde product **1b** was determined by X-ray crystallographic analysis (see ORTEP drawing, Figure 1)<sup>9</sup> of the corresponding carbamate **1c** (mp 149–153 °C, EtOAc/hexanes), prepared by sodium borohydride reduction of **1b**, followed by reaction of the resulting alcohol with *p*-bromophenyl isocyanate (72% overall yield). The absolute configuration (*S*) of the stereogenic center formed in this reaction (**1a**→**1b**) using (*2R,5R*)-**A**

**Table 1.** Screening of Reaction Conditions for the Intramolecular  $\alpha$ -Arylation<sup>a</sup>

Entry	Solvent	Additive	Yield <sup>b</sup>	ee <sup>c</sup>
1	acetone	H <sub>2</sub> O	75	89
2	THF	H <sub>2</sub> O	67	92
3	MeCN	H <sub>2</sub> O	16	85
4	DME	H <sub>2</sub> O	80	94
5	CH <sub>2</sub> Cl <sub>2</sub>	H <sub>2</sub> O	NR	
6	DME	none	46	95
7	DME	NaHCO <sub>3</sub>	77	91
8	DME	NaHCO <sub>3</sub> + H <sub>2</sub> O	46	95
9	DME	DTBP + H <sub>2</sub> O	64	94
10	DME	NaOAc + H <sub>2</sub> O	60	95

<sup>a</sup> Reactions were performed on 0.25 mmol scale using 20 mol % of catalyst (*2R,5R*)-**A**, 20 mol % of TFA, 2.0 equiv of CAN, and 2.0 equiv of additive in the specified solvent (4.0 mL) at –30 °C for 24 h. <sup>b</sup> Yield obtained after flash chromatography. <sup>c</sup> Determined by HPLC analysis on chiral stationary phase of corresponding alcohols obtained by NaBH<sub>4</sub> reduction.



**Figure 1.** X-ray derived ORTEP drawing of compound **1c**.

indicates that the intramolecular attack from the aromatic nucleus occurs from the *Si* face of the enamine intermediate formed in the catalytic cycle (vide infra).

Having established the optimum conditions for the reaction and its absolute stereochemical course, we then proceeded to investigate its generality and scope. As demonstrated in Table 2, a series of aldehydes incorporating an electron-rich aromatic system enter the cyclization reaction in good to excellent yield. The likely catalytic cycle for this reaction is depicted in Scheme 1 for substrate **2a**. Thus enamine activation of aldehyde **2a** by amine (*2R,5R*)-**A** is followed by single-electron transfer oxidation of the resulting enamine **B** by CAN to afford the highly reactive radical cation **C** [**C**↔**C**<sup>•+</sup>] which rapidly collapses intramolecularly to Wheland- or  $\sigma$ -complex **D**,<sup>10</sup> a characteristic intermediate in typical Friedel–Crafts reactions. This more stable species then loses a proton (**D**→**E**) and undergoes a second single-electron transfer oxidation with CAN to afford iminium species **F**. Finally, hydrolysis of **F** affords aldehyde **2b** and catalyst (*2R,5R*)-**A** which enters back into the catalytic cycle.

As a demonstration of the power of this catalytic asymmetric reaction, we developed a short and efficient total synthesis of the

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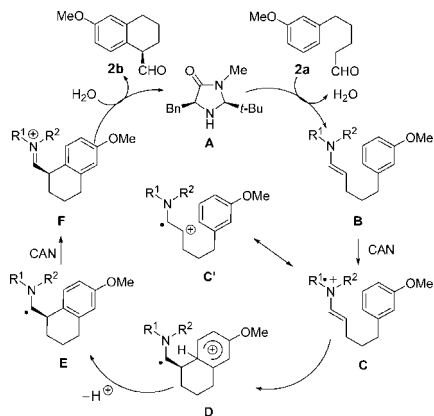
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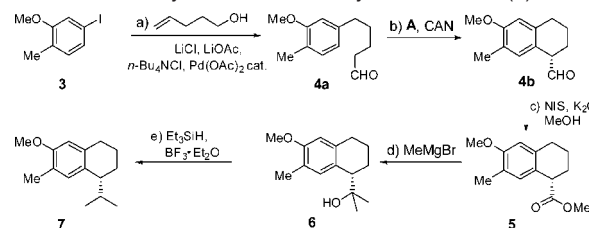
**Table 2.** Generality and Scope of the Intramolecular Friedel–Crafts  $\alpha$ -Arylation<sup>a</sup>

Entry	Substrate	Product	Yield <sup>b</sup>	ee <sup>c</sup>
1			80	94
2			76	86
3			77	97
4			76	87
5			64	98
6			55	94 <sup>d</sup>
7			58	94
8			54	84 <sup>d</sup>
9			51	85
10			52	92

<sup>a</sup> Reactions were performed on 0.25 mmol scale using 20 mol % of catalyst (2*R*,5*R*)-**A**, 20 mol % of TFA, 2.0 equiv of CAN, and 2.0 equiv of H<sub>2</sub>O in DME (4.0 mL) at -30 °C for 24 h. <sup>b</sup> Isolated yield after flash column chromatography. <sup>c</sup> Determined by HPLC analysis on chiral stationary phase of the corresponding alcohols obtained by NaBH<sub>4</sub> reduction. <sup>d</sup> Determined by HPLC analysis on chiral stationary phase of the corresponding Naproxen ester.

**Scheme 1.** Proposed Catalytic Cycle of the Intramolecular Friedel–Crafts  $\alpha$ -Arylation

antitumor natural product demethyl calamenene (**7**, Scheme 2).<sup>11</sup> Thus, Heck reaction between aryl iodide<sup>12</sup> **3** and 4-penten-1-ol [Pd(OAc)<sub>2</sub> cat., *n*-Bu<sub>4</sub>NCl, LiOAc·2H<sub>2</sub>O, LiCl]<sup>13</sup> afforded aldehyde **4a** in 63% yield. Reaction of this aldehyde under the developed conditions led to bicyclic aldehyde **4b** (56% yield, 90% ee). One pot oxidation/esterification with NIS, K<sub>2</sub>CO<sub>3</sub>, and MeOH in MeCN

**Scheme 2.** Total Synthesis of Demethyl Calamenene (**7**)<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) 4-penten-1-ol (1.1 equiv), Pd(OAc)<sub>2</sub> (3 mol %), *n*-Bu<sub>4</sub>NCl (2.0 equiv), LiOAc·2H<sub>2</sub>O (3.0 equiv), LiCl (1.0 equiv), DMF, 25 °C, 72 h (63%); (b) catalyst (2*R*,5*R*)-**A** (20 mol %), CAN (2.0 equiv), H<sub>2</sub>O (2.0 equiv), DME (0.0625 M), -30 °C, 24 h (56%, 90% ee); (c) NIS (3.1 equiv), K<sub>2</sub>CO<sub>3</sub> (3.1 equiv), MeOH (104 equiv), MeCN, dark, 25 °C, 24 h (84%); (d) MeMgBr (3 M in ether, 2.0 equiv), THF, 0→-25 °C, 16 h (65%); (e) Et<sub>3</sub>SiH (5.0 equiv), BF<sub>3</sub>·Et<sub>2</sub>O (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -10 to -5 °C, 1 h (87%).

furnished methyl ester **5** in 84% yield.<sup>14</sup> Exposure of the latter compound to MeMgBr in THF provided alcohol **6** (65% yield), whose reductive deoxygenation with Et<sub>3</sub>SiH in the presence of TFA led to synthetic demethyl calamenene (**7**) in 87% yield. The physical data for synthetic **7** matched those previously reported for the natural product.<sup>11</sup>

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**Supporting Information Available:** Experimental procedures and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) See the Supporting Information for the preparation of **1c**. CCDC 709588 contains the supplementary crystallographic data for **1c** and is available free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- (10) In view of the requirement of electron donating substituents on the aromatic nucleus for this reaction, we favored the cationic rather than the radical mechanism operating in the corresponding reactions with alkenes (see refs 1 and 2).
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