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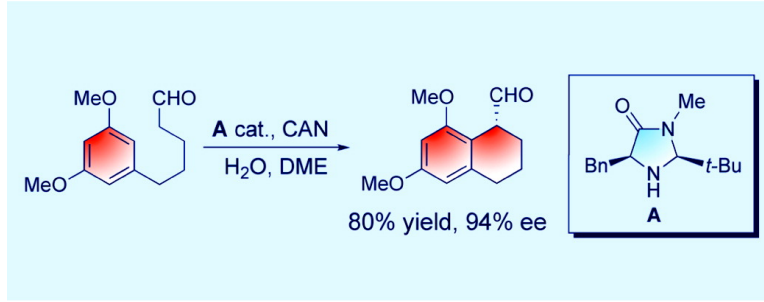

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Enantioselective Intramolecular Friedel−Crafts-Type α-Arylation of Aldehydes

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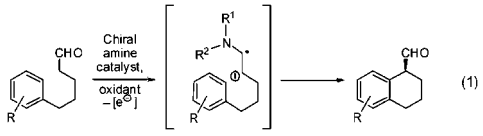
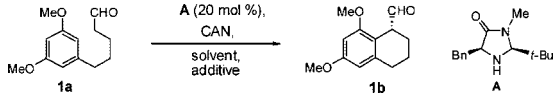
Enantioselective organo-SOMO catalysis has, in the last two years, been the subject of considerable development and exploration. A number of new and unique transformations have been reported, such as α-allylation,[1a] α-oxyamination,[2] α-enolation,[1b] and α-vinylation,[3] of aldehydes. Herein, we report a modification of this activation mode that involves the intramolecular Friedel−Crafts type α-arylation of aldehydes[4] carrying electron-donating groups on their aromatic nucleus (eq 1) and its application to the total synthesis of demethyl calamenene (**7**, Scheme 2),[5] 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.[6] Proline-[7] and diphenylprolinol-based[8] 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 ((2*R*,5*R*)-**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)[9] 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 (2*R*,5*R*)-**A** 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).

Table 1. Screening of Reaction Conditions for the Intramolecular α-Arylation[a]



Entry	Solvent	Additive	Yield[b]	*ee*[c]
1	acetone	H_2O	75	89
2	THF	H_2O	67	92
3	MeCN	H_2O	16	85
4	DME	H_2O	80	94
5	CH_2Cl_2	H_2O	NR	
6	DME	none	46	95
7	DME	$NaHCO_3$	77	91
8	DME	$NaHCO_3$ + H_2O	46	95
9	DME	DTBP + H_2O	64	94
10	DME	NaOAc + H_2O	60	95

[a] 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 additive in the specified solvent (4.0 mL) at −30 °C for 24 h. [b] Yield obtained after flash chromatography. [c] Determined by HPLC analysis on chiral stationary phase of corresponding alcohols obtained by $NaBH_4$ reduction.

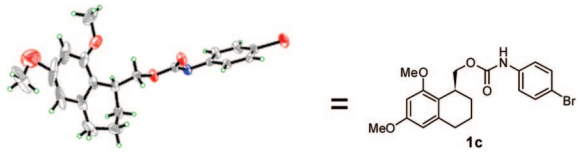


Figure 1. X-ray derived ORTEP drawing of compound **1c**.

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 (2*R*,5*R*)-**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′**] which rapidly collapses intramolecularly to Wheland- or *σ*-complex **D**,[10] 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 (2*R*,5*R*)-**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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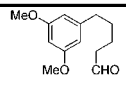
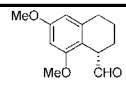
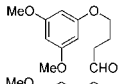
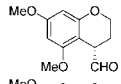
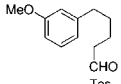
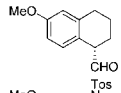
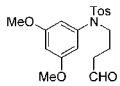
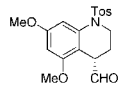
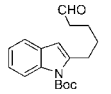
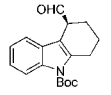
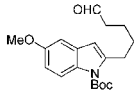
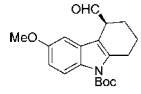
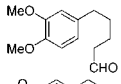
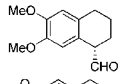
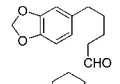
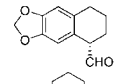
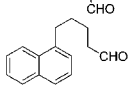
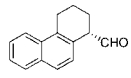
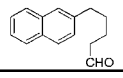
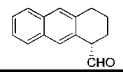
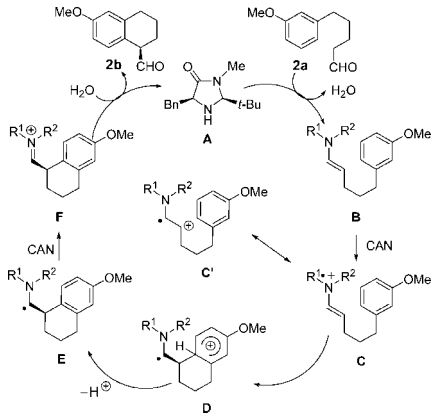
Table 2. Generality and Scope of the Intramolecular Friedel–Crafts α-Arylation[a]

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

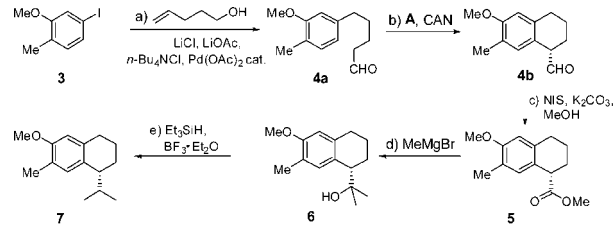
[a] Reactions were performed on 0.25 mmol scale using 20 mol % of catalyst (2*R*,5*R*)-**A**, 20 mol % of TFA, 2.0 equiv of CAN, and 2.0 equiv of H_2O in DME (4.0 mL) at −30 °C for 24 h. [b] Isolated yield after flash column chromatography. [c] Determined by HPLC analysis on chiral stationary phase of the corresponding alcohols obtained by $NaBH_4$ reduction. [d] Determined by HPLC analysis on chiral stationary phase of the corresponding Naproxen ester.

Scheme 1. Proposed Catalytic Cycle of the Intramolecular Friedel–Crafts α-Arylation



antitumor natural product demethyl calamenene (**7**, Scheme 2).[11] Thus, Heck reaction between aryl iodide[12] **3** and 4-penten-1-ol [$Pd(OAc)_2$ cat., *n*-Bu_4NCl, $LiOAc\cdot 2H_2O$, LiCl][13] 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_2CO_3, and MeOH in MeCN

Scheme 2. Total Synthesis of Demethyl Calamenene (**7**)[a]



[a] Reagents and conditions: (a) 4-penten-1-ol (1.1 equiv), $Pd(OAc)_2$ (3 mol %), *n*-Bu_4NCl (2.0 equiv), $LiOAc\cdot 2H_2O$ (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_2O (2.0 equiv), DME (0.0625 M), −30 °C, 24 h (56%, 90% ee); (c) NIS (3.1 equiv), K_2CO_3 (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_3SiH (5.0 equiv), $BF_3\cdot Et_2O$ (3.0 equiv), CH_2Cl_2, −10 to −5 °C, 1 h (87%).

furnished methyl ester **5** in 84% yield.[14] Exposure of the latter compound to MeMgBr in THF provided alcohol **6** (65% yield), whose reductive deoxygenation with Et_3SiH 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.[11]

Acknowledgment. We thank Professor Charles L. Perrin for insightful discussions and Drs. D. H. Huang, G. Siuzak, R. Chadha for NMR spectroscopic, mass spectrometric, and for X-ray crystallographic assistance, respectively. This work was supported by the National Science Foundation (CHE-0603217), the Skaggs Institute for Research, and the Deutscher Akademischer Austausch Dienst (fellowship to R.R.).

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.
(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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