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The Enantioselective Organocatalytic 1,4-Addition of Electron-Rich Benzenes to α,β-Unsaturated Aldehydes

Nick A. Paras and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

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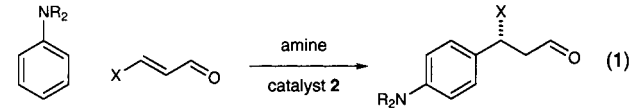
One of the most important chiral synthons throughout the realm of organic architecture is represented by the benzylic carbon stereocenter. Found in over 5000 natural product isolates,[1] this stereochemical motif has also gained a "privileged" status in medicinal chemistry due to its recurring presence among therapeutic agents (e.g., Zoloft,[2] Paxil,[3] Detrol[4]). While catalytic access to enantioenriched benzylic architecture has been accomplished with hydrogenation[5] or metallobenzene addition technologies,[6] a complimentary approach might involve the enantioselective alkylation of benzene rings with electron deficient olefins.[7] In this context, we have recently reported that the LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of iminium ions is a valuable platform for the development of enantioselective cycloadditions[8] and heteroaromatic substitutions.[9] In this communication, we further advance this iminium activation strategy to achieve the first enantioselective organocatalytic alkylation of aniline rings (eq 1). Importantly, this strategically new approach to asymmetric conjugate addition allows the construction of complex benzylic carbon stereogenicity with simple α,β-unsaturated aldehydes and aryl substrates.

Organocatalytic Aniline Conjugate Addition



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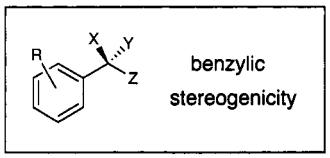
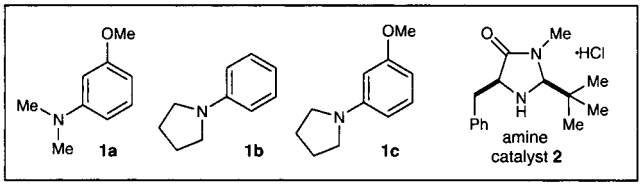
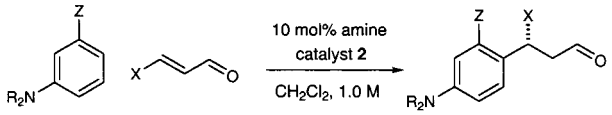


- Common natural product subunit, >5000 examples
- Privileged structural motif in medicinal chemistry

Our enantioselective organocatalytic benzene alkylation was first evaluated with anilines **1a**−**c**, imidazolidinone catalyst **2**, and a series of α,β-unsaturated aldehydes (Table 1). Initial investigations revealed that the (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-imidazolidinone catalyst **2** (10 mol %, CH_2Cl_2) promotes the addition of *N*,*N*-dimethyl-3-anisidine (**1a**) and *N*-phenyl pyrrolidine (**1b**) to crotonaldehyde with high levels of enantioselectivity (entries 1 and 2, 70−86% yield, 87−89% ee). As revealed in Table 1, variation in the steric contribution of the olefin substituent (X = Me, Et, CH_2OBz, entries 1−5) is possible without substantial loss in yield or enantiocontrol (68−89% yield, 87−92% ee). There appears to be broad scope in the electronic nature of the α,β-unsaturated aldehyde component. For example, the reaction can accommodate enals that do not readily participate in iminium formation (entry 6, X = CO_2Me, 90% yield, 92% ee), as well as aldehydes that provide stable iminium intermediates (entry 7, X = Ph, 82% yield, 84% ee). A variety of

Table 1. Organocatalyzed Alkylation of Anilines **1a**, **1b**, and **1c** with Representative α,β-Unsaturated Aldehydes





entry	aniline	X	temp(°C)	time(h)	% yield	% ee[a]
1	**1a**	Me	−40	36	86	89[d]
2	**1b**	Me	−20	48	70[b]	87[d]
3	**1a**	Et	−50	48	68	88[d]
4	**1a**	CH_2OBz[c]	−20	24	89	92[d]
5	**1b**	CH_2OBz[c]	+20	24	73	90[d]
6	**1a**	CO_2Me[c]	−20	8	90	92[d]
7	**1c**	Ph	−50	36	82[b]	84
8	**1c**	*p*-Cl-Ph	−50	80	80[b]	92
9	**1a**	*p*-NO_2-Ph	−10	48	87	92
10	**1b**	*p*-NO_2-Ph	+20	48	82	90

[a] Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b] Using 20 mol % catalyst. [c] 1.0 M in $CHCl_3$. [d] Absolute configuration assigned by chemical correlation.

β-aromatic substituents on the olefin can be employed to construct bis-benzylic stereogenicity, a structural motif commonly found among drug candidates[2,4] that is not readily accessible via asymmetric hydrogenation[10] (entries 7−10, 80−85% yield, 84−92% ee).

Significant structural variation in the aniline component can also be realized (Table 2). The reaction appears quite general with respect to the nature of the nitrogen substituents (entries 1−8, NMe_2, NBn_2, 1-pyrrolidino, indoline, 93−99% ee). Initial studies have revealed that the pyrrolidino-benzene and indoline rings are significantly more reactive than the *N*,*N*-dimethyl or *N*,*N*-dibenzyl anilines (cf. entries 2, 3, 5, and 8, k_{rel} pyrrolidino:indoline:NMe_2:NBn_2 = 48:48:4:1). As revealed in Table 2, a variety of alkyl and heteroatom substituents can be incorporated on the aniline ring at both the ortho and meta positions without loss in reaction efficiency or enantiocontrol (entries 6−13, R_1 or R_2 = Ph, Me, OMe, SMe, 84−99% ee). Moreover, the aryl framework can be successfully extended to naphthalene-derived systems (entry 9, 93% ee). We have also utilized relatively electron deficient anilines in the context of a 3-chloro-substituted ring (entry 14, 73% yield, 93% ee). Such halogenated benzene adducts should prove to be valuable synthons for use in conjunction with organometallic technologies (e.g., Stille[11]

* Corresponding author. E-mail: dmacmill@caltech.edu.

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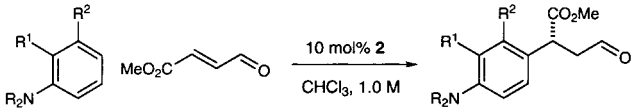
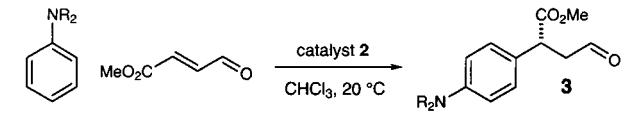
Table 2. Organocatalyzed Alkylation of Methyl 4-Oxobutenoate with Representative Anilines



entry	NR_2	R^1	R^2	temp(°C)	time(h)	% yield	% ee[a]
1	NMe_2	H	H	–10	48	86	96[b]
2	NMe_2	H	H	+20	5	77	94[b]
3	NBn_2	H	H	+20	24	65	96[b]
4	1-pyrrolidino	H	H	–20	8	97	97[b]
5	1-pyrrolidino	H	H	+20	0.3	96	95[b]
6	1-pyrrolidino	Ph	H	+20	12	94	99
7	–N(Me)CH_2CH_2–		H	–20	8	94	98
8	–N(Me)CH_2CH_2–		H	+20	0.3	93	93
9	NMe_2	–CH=CH-CH=CH–		+20	36	89	93
10	NMe_2	H	Me	–10	10	89	84[b]
11	NMe_2	H	OMe	–20	8	90	92[b]
12	NMe_2	H	OMe	+20	0.1	73	91[b]
13	NMe_2	H	SMe	–20	8	92	91
14	NMe_2	H	Cl	–20	80	73	93[b,c]
15	NMe_2	H	Cl	+20	12	66	86[b]

[a] Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b] Absolute configuration assigned by chemical correlation. [c] Using catalyst **2** (20 mol % amine, 15 mol % HCl).

Table 3. Effect of Catalyst Loading on Organocatalyzed Alkylations



entry	mol% catalyst **2**	time	% yield[a]	% ee[b]
1	10	20 min	96	95
2	5	2 h	92	94
3	2	12 h	92	92
4	1	40 h	87	88

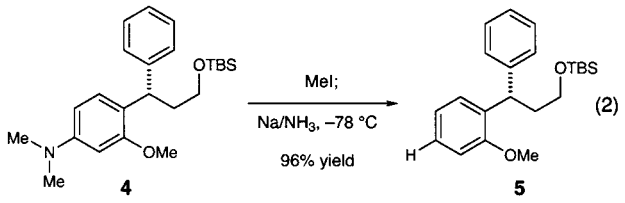
[a] NR_2 = 1-pyrrolidino. [b] Ratios determined by chiral HPLC.

and Suzuki couplings[12−13]). As expected, subambient temperatures (−10 to −20 °C) provide optimal levels of asymmetric induction (91−98% ee); however, alkylations conducted at room temperature provide operationally convenient reaction times without significant loss in enantioselectivity (e.g., entries 1 and 2, −10 °C, 96% ee, 48 h; 20 °C, 94% ee, 5 h). It should be noted that only products arising from regioselective alkylation of the aniline para position were observed throughout this study.

The effect of catalyst loading on reaction efficiency has been evaluated (Table 3). While 10 mol % of imidazolidinone **2** was routinely employed in this investigation, it appears that catalyst loadings as low as 1 mol % provide useful levels of enantioselectivity (10 mol % **2**, 95% ee; 1 mol % **2**, 88% ee). Preliminary kinetic studies have revealed that the observed change in reaction rate as a function of catalyst loading is consistent with second-order kinetics in the amine·HCl component. To demonstrate preparative utility, the addition of *N*-phenyl pyrrolidine to methyl 4-oxobutenoate was performed on a 50 mmol scale with 2 mol % of catalyst **2** (240 mg) to afford 12.2 g (97% yield) of the aniline adduct (*R*)-**3** in 92% ee (87% yield, 96% ee after recrystallization).

With regard to the synthetic and operational advantages of these organocatalytic alkylations, it is important to note that (i) the sense of asymmetric induction observed in all cases was readily anticipated by the previously described model[9b] and (ii) all of the alkylations described herein were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench stable catalyst.

Last, we have recently developed a new sequence for the direct deamination of *N*,*N*-dialkyl aniline rings. As revealed in eq 2, treatment of aniline **4** with methyl iodide followed by exposure of the resulting quaternary amine to reductive conditions provides the parent aromatic system **5** in excellent yield. Importantly, this operationally simple protocol effectively enables dialkylanilines to be employed as benzene surrogates in this new organocatalytic alkylation strategy.



In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of enantioselective benzene alkylations. Further studies to determine the utility of amine catalyst **2** are underway.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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