New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedel−Crafts Alkylation

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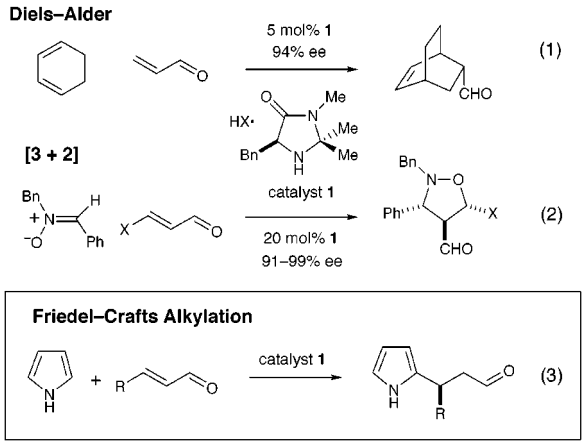
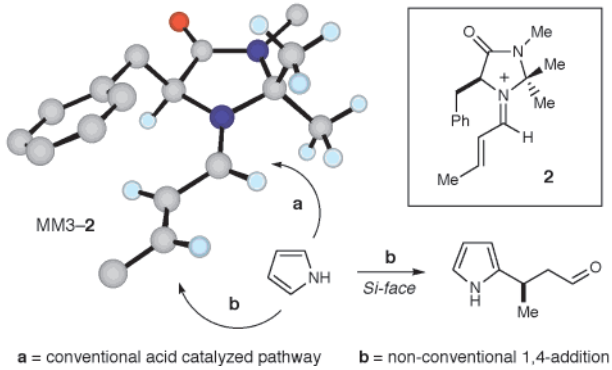
The metal-catalyzed addition of aromatic substrates to electron deficient σ- and π-systems, commonly known as Friedel−Crafts alkylation,[1] has long been established as a powerful strategy for C−C bond formation.[2] Surprisingly, however, relatively few asymmetric catalytic protocols have been reported that exploit this venerable reaction manifold,[3] despite the widespread availability of electron-rich aromatics and the chemical utility of the accompanying products. In our recent studies, we reported that the LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of iminium ions with chiral imidazolidinone **1**[4] is a valuable platform for the development of enantioselective organocatalytic Diels−Alder reactions[5] (eq 1) and [3 + 2] nitrone cycloadditions[6] (eq 2). In this communication, we

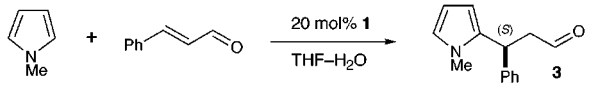


demonstrate that this organocatalytic strategy is also amenable to the enantioselective Friedel−Crafts alkylation of pyrroles with α,β-unsaturated aldehydes to generate β-pyrrolyl carbonyls (eq 3), useful synthons for the construction of a variety of biomedical agents.[7] To our knowledge this study represents the first example of an enantioselective conjugate pyrrole addition using chiral amine or metal catalysts.



To further demonstrate the value of our iminium-catalysis strategy, we recently sought to develop an asymmetric Friedel−Crafts variant that is currently unavailable using acid or metal catalysis. In this context, it has been documented that α,β-unsaturated aldehydes are poor electrophiles for pyrrole conjugate addition due to the capacity of electron-rich aromatics to undergo acid-catalyzed 1,2-carbonyl addition.[8] As illustrated with the calculated iminium ion model MM3−**2**,[9] we expected α,β-unsaturated iminium ions arising from chiral amine **1** to be inert to 1,2-addition (pathway **a**) on the basis of steric constraints imposed by the catalyst framework. As such, we assumed that catalyst **1** might selectively partition heteroaromatic nucleophiles toward a nonconventional and less sterically demanding 1,4-addition manifold (pathway **b**) while enforcing high levels of enantiocontrol in the carbon−carbon bond forming event.

Table 1. Effect of the Brønsted Acid Cocatalyst on the Friedel−Crafts Alkylation of Cinnamaldehyde with *N*-Methyl Pyrrole



entry	H–X cocatalyst	Temp (°C)	Time (h)	% yield[a]	% ee[b,c]
1	$NCCH_2CO_2H$ (**1a**)	23	32	10	80
2	Cl_2CHCO_2H (**1b**)	23	32	62	80
3	Cl_3CCO_2H (**1c**)	23	3	64	81
4	TFA (**1d**)	23	3	78	81
5	TFA (**1d**)	−30	42	87	93

[a] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction. [b] Product ratios determined by chiral GLC. [c] Absolute configuration assigned by chemical correlation to a known compound.

Our enantioselective catalytic Friedel−Crafts alkylation was first evaluated using *N*-methyl pyrrole with (*E*)-cinnamaldehyde and a series of benzyl imidazolidinone·HX salts **1**. As revealed in Table 1, this reaction was successful with a variety of amine catalysts (entries 1−5) to provide the desired conjugate addition adduct with moderate to excellent enantioselectivity (80−93% ee).[10] It is important to note that products arising from 1,2-iminium addition were not observed in these reactions, in accord with our

(1) Friedel, C.; Crafts, J. M. *Bull. Soc. Chim. Fr.* **1877**, *27*, 530.
(2) (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.8, p 293. (b) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984. (c) *Friedel-Crafts Chemistry*; Olah, G. A., Ed.; Wiley: New York, 1973. (d) *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1963−65; Vols. 1−4.
(3) (a) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Saaby, S.; Fang, X. M.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (c) Jensen, K. M.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.
(4) Derived in two steps from (*S*)-phenylalanine.
(5) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(6) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
(7) (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Thieme: Stuttgart; New York, 2001. (b) (*S*)-Ketorolac: Guzman, A.; Yuste, F.; Toscano, R. A.; Young, J. M.; Vanhorn, A. R.; Muchowski, J. M. *J. Med. Chem.* **1986**, *29*, 589. (c) Viminol: Della Bella, D. *Boll. Chim. Farm.* **1972**, *111*, 5.
(8) (a) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer-Verlag: Heidelberg, 1999; Vol 3. (b) Strell, A.; Kalojanoff, R. *Chem. Ber.* **1954**, *87*, 1954.
(9) Monte Carlo simulation, MM3 force-field; Macromodel V6.5.
(10) A broad range of Brønsted acid cocatalysts have been evaluated: HCl, 77% ee; *p*-TSA, 42% ee; TfOH, 55% ee.

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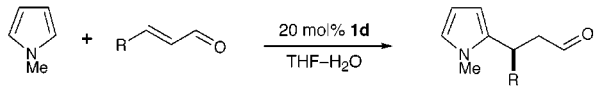
Table 2. Organocatalyzed Friedel−Crafts Alkylation between *N*-Methyl Pyrrole and Representative α,β-Unsaturated Aldehydes



entry	R	temp (°C)	time (h)	% yield[a]	% ee[b,c]
1	Me	−60	72	83	91[d]
2	Pr	−50	72	81	90
3	*i*-Pr	−50	72	80	91
4	Ph	−30	42	87	93
5	4-MeOPh	−30	104	79	91
6	CH_2OBn	−60	72	90	87[d]
7	CO_2Me	−50	104	72	90[e]

[a] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction. [b] Ratios determined by chiral GLC or HPLC. [c] Absolute stereochemistry determined by chemical correlation or by analogy. [d] Using 10 mol % catalyst **1d**. [e] Using catalyst **1a**.

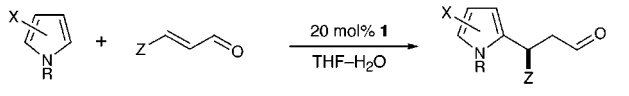
mechanistic postulate. An enantioselectivity/temperature profile documents that optimal enantiocontrol is achieved with catalyst **1d** at −30 °C to afford substituted pyrrole (*S*)-**3** in 93% ee and 87% yield (entry 5). The superior levels of asymmetric induction and reaction efficiency exhibited by the TFA salt **1d** prompted us to select this catalyst for further exploration.

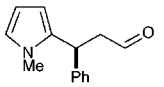
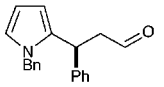
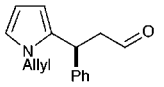
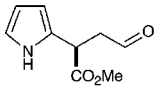
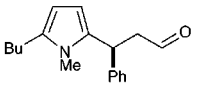
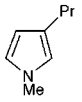
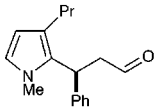
The scope of the organocatalytic Friedel−Crafts alkylation between *N*-methyl pyrrole and various α,β-unsaturated aldehydes has been investigated (Table 2). Significant variation in the steric contribution of the olefin substituent (R = Me, Pr, *i*-Pr, entries 1−3) is possible without loss in yield or enantioselectivity (≥80% yield, ≥90% ee). The reaction is also tolerant of β-aromatic substituents on the olefin component (entries 4−5, ≥79% yield, 91−93% ee). As revealed in entries 6 and 7, the reaction can accommodate electron-deficient aldehydes that do not readily participate in iminium formation (R = CH_2OBn, 87%ee; R = CO_2Me, 90% ee). To demonstrate the preparative utility, the addition of *N*-methyl pyrrole to cinnamaldehyde was performed on a 25 mmol scale with catalyst **1d** to afford (*S*)-**3** in 93% ee and 87% yield.

This amine-catalyzed Friedel−Crafts alkylation is also general with respect to pyrrole architecture (Table 3). Variation in the *N*-alkyl group (R_1 = H, Me, Bn, allyl, entries 1−4) is possible without loss in yield or enantioselectivity (≥74% yield, 89−93% ee). Incorporation of alkyl substituents at the C(2)-pyrrole position reveals that increased π-nucleophilicity has little influence on reaction selectivity (entry 5, 87% yield, 90% ee).[11,12] In accordance with established heteroaromatic addition methodology,[8a] the use of C(3)-substituted pyrroles results in regioselective alkylation of the more hindered C(2)-aromatic site (entry 6, 98:2 C(2):C(5) selectivity) with excellent levels of enantiocontrol (97% ee).

A further illustration of the utility of this organocatalytic Friedel−Crafts alkylation is presented in the reaction of *N*-methyl pyrrole with excess crotonaldehyde (eq 4). The central issue in this reaction is that of catalyst-controlled alkylation at both C(2) and C(5) of the aromatic nucleophile to provide enantioselective access to C_2-symmetric pyrrole adducts. As outlined in eq 4, formation of the 2,5-disubstituted pyrrole **4** is accomplished in 98% ee and 90:10 selectivity for the desired C_2-isomer (83% yield). This concept can be further advanced to the implementation of two discrete α,β-unsaturated aldehydes to provide the non-symmetrical disubstituted pyrrole **5** in 99% ee and 90:10 *anti* selectivity (eq 5, 72% yield over two steps). Interestingly, we expect this enantioselective bisalkylation technology to be of particular value for the construction of ligands for use in asymmetric organometallic catalysis.

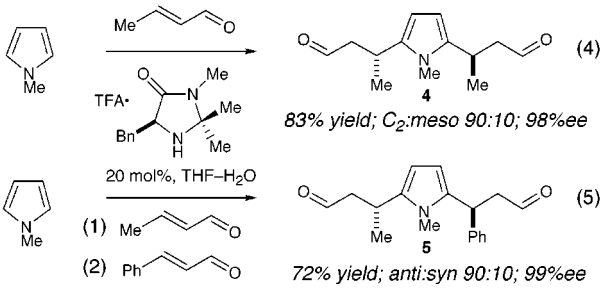
Table 3. Organocatalyzed Friedel−Crafts Alkylation between α,β-Unsaturated Aldehydes and Representative Pyrroles



entry	pyrrole	Z	product	yield[a]	% ee[b,c]
1		Ph		87	93[d]
2		Ph		80	89[e]
3		Ph		83	91[e]
4		CO_2Me		74	90[f]
5		Ph		87	90[e]
6		Ph		68	97[c]

[a] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction. [b] Ratios determined by chiral GLC or HPLC. [c] Absolute stereochemistry determined by chemical correlation or by analogy. [d] Using catalyst **1d**. [e] Using catalyst **1c**. [f] Using catalyst **1a**.

Finally, with regard to the operational advantages of organocatalysis, it is important to note that (i) the sense of asymmetric induction observed in all cases was readily anticipated by the calculated iminium ion model MM3−**2** in accord with previous studies,[5,6] and (ii) all of the alkylations described herein were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst.



In summary, we have further established LUMO-lowering organocatalysis as a broadly useful concept for asymmetric synthesis in the context of the Friedel−Crafts alkylation. A full account of this survey will be forthcoming.

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

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(11) Only products arising from regioselective alkylation of the pyrrole C(5) position were observed in these cases.

(12) Aromatic systems that are electron-deficient relative to pyrrole were found to be poor substrates for these alkylation reactions. A new organocatalytic Friedel−Crafts protocol that is specifically selective for indoles, furans, and thiophenes has recently been developed in our laboratory and will be reported in due course.