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Highly Enantioselective Friedel−Crafts Alkylations of Pyrroles and Indoles with α′-Hydroxy Enones under Cu(II)-Simple Bis(oxazoline) Catalysis

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The Friedel−Crafts reaction of arenes with electron-deficient alkenes is an important C−C bond-forming process in organic synthesis.[1] While asymmetric catalytic versions of this reaction provide access to important enantioenriched aryl-substituted products, only a few examples of such processes are known:[2] (a) the reaction of enals **1** with pyrroles and indoles catalyzed by a chiral secondary amine catalyst,[3] and (b) the metal-catalyzed reactions involving β,γ-unsaturated α-ketoesters **2**,[4] alkylidene malonates **3**,[5] and acyl phosphonates **4**.[6] Friedel−Crafts reactions with two additional alkene templates, **5** and **6**, have also been described[7] but with more limited results. Yet, important restrictions apply to substrate generality and reaction selectivity. Apparently, in metal-catalyzed Friedel−Crafts reactions not only bidentate, chelating Michael acceptors are required but also particularly effective metal−substrate coordination is needed for optimum selectivity.[8] Previous observations from this laboratory in the context of Diels−Alder[9] and conjugate addition[10] reactions have shown the capability of α′-hydroxy enones for metal-assisted activation, likely through formation of 1,4-metal chelated species as the reactive intermediates. On this basis, we pursued to validate such a 1,4-metal binding hypothesis[11] and, hence, increase the pool of available templates for catalytic, asymmetric Friedel−Crafts reactions. Since the pyrrole and indole skeletons are important substructures within natural product isolates and medicinal agents,[12]these heteroarenes were selected for the study. Initial screening reactions carried out with enone **7a** and *N*-methyl pyrrole **8** in the presence of 10 mol % of a survey of chiral bis(oxazoline)−metal complexes in CH_2Cl_2 as solvent, revealed **12** and **13** as the most effective.[13] Using these catalysts, Friedel−Crafts adduct **10a** was formed in yields of 86 and 80% and, most notably, with 92 and 91% ee, respectively. With the exception of β-aryl enones, such as **7g**, which provided product **10g** with modest enantioselectivity, good yields and excellent enantiomeric excesses were obtained with a series of enones (**7a**−**f**) which vary in the identity of the β-alkyl substituent (Table 1). In some instances, small amounts of dialkylation product were detected,[14] which could be partially or totally suppressed by lowering the temperature and increasing the mole equivalents of **8**, respectively. The system also proved effective for the reactions of *N*−*H* pyrrole **9** to give adducts **11**.

Indole derivatives **14**−**17** worked as efficiently as pyrroles and provided adducts **18**−**21** in good to excellent yields and enantiomeric excesses (Table 2). While the typical reaction temperature was either 0 or 25 °C, the catalytic system showed remarkable performance even at refluxing conditions (40 °C) (entries 3 and 7). Enones bearing branched chains at the β position showed attenuated reactivity and lower selectivity using catalyst **12**, but using catalyst **13**,[15] high enantiomeric excesses could be attained (entry 6, from 85 to 93%; entry 9, from 85 to 96%). Importantly, increasing the scale (entry 1) and lowering the catalyst loading to 5 and 2 mol % (entries 2 and 4), which represents the lowest catalyst/substrate ratio employed in the asymmetric Friedel−Crafts reaction,[4] resulted in no significant loss of enantioselectivity and yield. Finally,[16] the reactions with differently substituted indoles **15**−**17** worked nicely.

Scheme 1. Alkene Templates **1**−**6** used in Asymmetric Catalytic Friedel−Crafts Alkylations and the New Development Based on Template **7** and Bis(oxazoline)−Cu(II) Catalysts

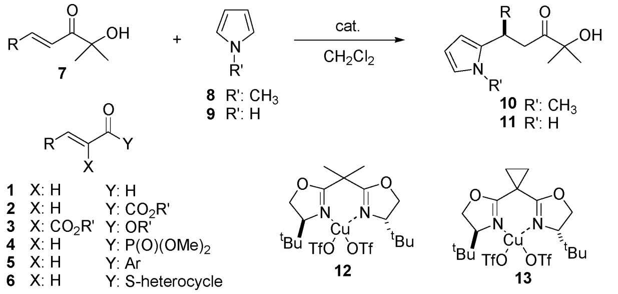

Table 1. Friedel−Crafts Alkylation of *N*-methyl Pyrrole **8** and Pyrrole **9** with Various α′-Hydroxy Enones **7** Catalyzed by Complex **12**[a]

enone **7**	R	*T*, °C	time, h	product	yield, %[b]	ee, %[c]
a	$PhCH_2CH_2$	25	2	**10a**	86	92
		25	2	**10a**	80	91[d]
		−20	2	**11a**	83	90
b	$CH_3(CH_2)_5$	−20	6	**10b**	82	96
		−20	0.5	**11b**	87	91[e]
c	$(CH_3)_2CH$	0	20	**10c**	86	95
d	*c*-C_6H_{11}	25	4	**10d**	84	97[f]
e	CH_3CH_2	−20	18	**10e**	88	94
f	$(CH_3)_2CHCH_2$	−20	12	**10f**	86	94[f]
g	Ph	25	24	**10g**	95	68[d]

[a] Reactions conducted at 0.5 mmol scale and 0.25 M substrate concentration. Mole ratio of arene:**7**:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] Using catalyst **13**. [e] Using 6 molar equiv of **9**. [f] Using 6 molar equiv of **8**.

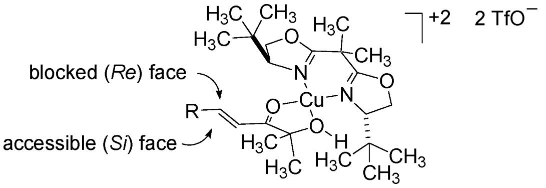

Figure 1. Stereochemical model for the substrate−catalyst complex.

The sense of asymmetric induction observed in the above reactions is consistent with the model shown in Figure 1, which assumes a distorted square planar geometry around copper, as previously disclosed in the literature for similar systems.[17]

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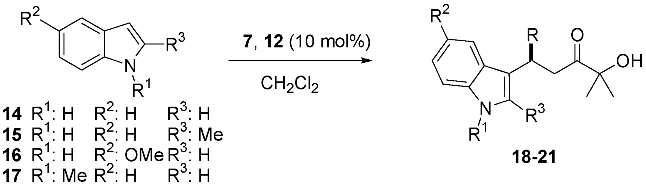
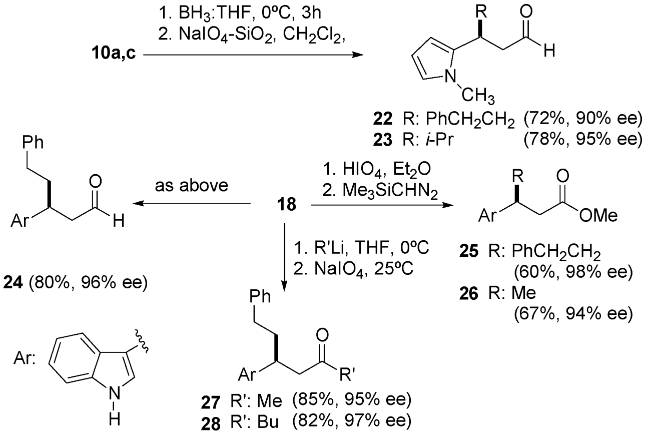
Table 2. Friedel−Crafts Alkylation of Indoles **14**−**17** with Various α′-Hydroxy Enones **7** Catalyzed by Complex **12**[a]



entry	indole		enone **7**, R	*T*, °C	time, h	product	yield, %[b]	ee, %[c]
1	**14**	**a**	PhCH$_2$CH$_2$	0	3	**18a**	88	95[d]
2				25	3		85	94[e]
3				reflux	0.5		85	98
4		**b**	CH$_3$(CH$_2$)$_5$	0	12	**18b**	85	96[f]
5		**c**	(CH$_3$)$_2$CH	25	48	**18c**	44[g]	85
6				25	24		68	93[h]
7				reflux	4		81	95
8		**d**	*c*-C$_6$H$_{11}$	25	36	**18d**	32[i]	85
9				25	24		80	96[h]
10		**h**	4-Cl−C$_6$H$_4$	0	48	**18h**	95	83[j]
11		**i**	CH$_3$	0	3	**18i**	65[i]	98
12	**15**	**a**	PhCH$_2$CH$_2$	25	2	**19a**	89	93
13	**16**	**a**	PhCH$_2$CH$_2$	25	2	**20a**	96	97
14	**17**	**a**	PhCH$_2$CH$_2$	25	2	**21a**	86	98

[a] Reactions conducted at 0.5 mmol scale and 0.25 M substrate concentration. Mole ratio of indole:**7**:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] Reaction conducted at 10 mmol scale. [e] Using 5 mol % catalyst loading. [f] Using 2 mol % catalyst loading. [g] Only 25% of unreacted enone **7c** recovered. [h] Using catalyst **13**. [i] Yield not optimized. [j] Using 30 mol % cat **13**.

Scheme 2. Elaboration of Adducts into Enantioenriched Pyrrole- and Indole-Substituted Aldehydes, Carboxylic Acids, and Ketones



The potential of this catalytic approach is best demonstrated by the versatile elaboration of adducts through oxidative cleavage of the ketol moiety. For example, adducts **10a**,**c** and **18a**, after sequential reduction and oxidative diol cleavage, afforded aldehydes **22**, **23**, and **24**, which were characterized as the corresponding alcohols. Alternatively, **18** could be transformed directly into carboxylic acids and, hence, esters **25** and **26** of high enantiomeric purity.[18] Of importance, a sequential alkyllithium addition to the carbonyl group in **18**, followed by treatment with NaIO$_4$, constituted a practical entry to the otherwise elusive ketone derivatives, such as **27** and **28**, in high yields and excellent enantioselectivities. Moreover, in these transformations, acetone is the only byproduct formed, an additional aspect of the approach that is of practical interest. In conclusion, α′-hydroxy enones **7** in combination with commercially available bis(oxazoline)−Cu(OTf)$_2$ catalysts significantly expand the enantioselective Friedel−Crafts reaction.

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Supporting Information Available: Complete experimental procedures, ^{1}H and ^{13}C spectra, HPLC chromatograms, crystallographic data for S-2 (CIF), and an ORTEP diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Olah, G. A.; Kishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339.
(2) For a review, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556. See also: (b) Jørgensen, K. A. *Synthesis* **2003**, 1117−1125.
(3) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895.
(4) Jensen, K. B.; Thorhauge, J.; Mazell, R.-G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163.
(5) (a) Zhuang, W.; Hausen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347−348. (b) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030−9031. (c) Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432−433. (d) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309−1320.
(6) Evans, D. A.; Scheidt, K. A.; Frandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781.
(7) (a) Bandini, M.; Fagioli, P.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511−7518. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753−3763.
(8) Widely used, chelating *N*-enoyl-2-oxazolidinones in combination with Cu(II)−BOX catalysts seemed to be totally ineffective; for example, unaltered starting materials are recovered after 2 days of stirring a mixture of *N*-methyl pyrrole and *N*-crotonyl-2-oxazolidinone in the presence of 10 mol % Cu(II)−*t*-BOX catalyst.
(9) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942−13943.
(10) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189.
(11) Hypothetically, the 1,4-metal arrangement resulting from the coordination of templates **2** and **4** with the catalyst is advantageous over the 1,5-metal arrangement encountered in other typical bidentate templates, such as **3**. Also, see ref 8.
(12) (a) Sundberg, R. D. Pyrroles and Their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984, Vol. 4, pp 313−376. (b) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559−590. (c) Toyota, M.; Ihara, N. *Nat. Prod. Rep.* **1998**, *15*, 327−340.
(13) Other solvents, such as THF, Et$_2$O, or toluene, tested using catalyst **12** led to slightly lower selectivity, while the reaction did not proceed at all in acetonitrile. See the Supporting Information for details.
(14) Enone/yield of dialkylated **8**: **7b**/4%, **7d**/14%, **7f**/8% (See SI for details).
(15) For enhancement of enantiomeric excess by ligand distortion, see: (a) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878. (b) Lipkowitz, K. B.; Schefzick, S.; Avnir, D. *J. Am. Chem. Soc.* **2001**, *123*, 6710−6711.
(16) Under the conditions reported, no reaction was observed between enone **7a** and other types of arenes tested, such as anisole and 3-dimethylaminoanisole.
(17) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335 and references therein. (b) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem.*−*Eur. J.* **2002**, *8*, 1888−1898.
(18) For assessment of the enantiomeric purity and the absolute configuration of the products, see the Supporting Information.

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