

Enantioselective Enolate Protonations: Friedel–Crafts Reactions with α -Substituted Acrylates**

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In recent decades, enantioselective protonation of prochiral enolates has become a practical means of accessing α -chiral carbonyl compounds with high enantiomeric purity.^[1] The majority of work in this area has focused on the enantioselective protonation of isolated enolate precursors, such as silyl enol ethers.^[2] Silyl enol ethers derived from α -substituted cyclic ketones have been most widely studied, owing to the fixed enolate geometry inherent in cyclic systems. Enantioselective protonations of acyclic enolate derivatives have also been developed, although to a lesser extent.^[2a,b,3] The involvement of acyclic enolates is more challenging, especially in the context of transient enolate generation, because strict control of enolate geometry is essential for enantioselectivity.

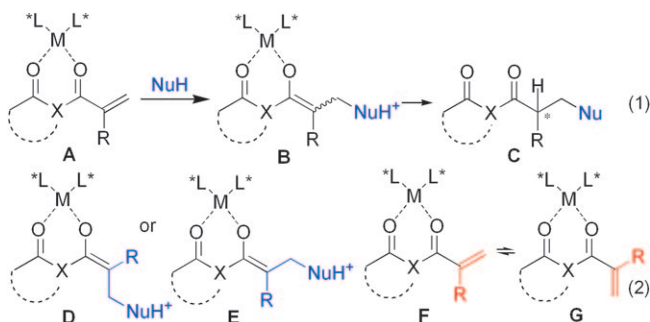
The issues associated with enantioselective protonation of acyclic enolates are directly relevant to tandem sequences involving a 1,4-addition of a nucleophile to an α -substituted α,β -unsaturated carbonyl compound, such as **A** (Scheme 1), followed by enantioselective protonation of the resulting transient enolate. Several tandem 1,4-addition/enantioselective protonation sequences have been reported for nitrogen,^[4] sulfur,^[5] phosphorous,^[5b] and carbon nucleophiles.^[6] However, these current sequences are somewhat limited and significant work remains necessary to access catalyst/substrate combinations that will prove general across nucleophile classes.

The use of carbon-based nucleophiles was of particular interest to us because C–C bond formation in 1,4-addition/

enantioselective protonation sequences is currently limited to rhodium-catalyzed additions of aryl boronic acids and potassium aryltrifluoroborates.^[6] Thus, we identified the Friedel–Crafts (F–C) reaction, one of the more important and widely studied C–C bond-forming reactions,^[7] as a valuable candidate for development of a 1,4-addition/enantioselective protonation process. However, only in the past decade have highly enantioselective variants^[8] using chiral Lewis acids^[9] or organocatalysts^[10] been reported for F–C alkylations of aromatic and heterocyclic nucleophiles with a variety of electrophilic acceptors. In all reported enantioselective F–C alkylations that use α,β -unsaturated carbonyl compounds as acceptors, the stereochemistry has been established at the β -carbon of the acceptor during the nucleophilic addition step. In contrast, there are no known examples wherein stereocenters are installed α to the carbonyl carbon, as it would require an enantioselective protonation step after nucleophile addition [**A** $\rightarrow$ **C**, Scheme 1, Eq. (1)], which would be possible only if the enolate formed with a single *E* or *Z* geometry [**D** or **E**, Scheme 1; Eq. (2)].

Based on our previous work with α -substituted acrylates in enantioselective transformations,^[11] our starting hypothesis was that rotamer control of the enoyl geometry (*s-cis* **F** or *s-trans* **G**) would impact both reactivity and enolate configuration. Thus, a judicious choice of an achiral template is important. Herein we report the first examples of highly enantioselective enolate protonation in Friedel–Crafts alkylations using pyrrole nucleophiles and α -substituted α,β -unsaturated imide electrophiles. Critical to the success of the tandem sequence is the development of a new achiral isoxazolidinone auxiliary which enhances reactivity and incorporates all the features necessary for efficient control of rotamer geometry.^[11e]

Our work began with the aim of identifying a combination of achiral template and chiral Lewis acid that provided high reactivity and selectivity in the model alkylation of *N*-methylpyrrole^[12] **5** (5 equivalents, to minimize the formation of the dialkylation product) with α -methyl acrylate acceptors (Table 1). After initial studies on the model reaction system (data not shown), we identified chiral Lewis acids prepared from the Ph-dbflox ligand^[13] **6** (Ph-dbflox = (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline)), and zinc(II) salts as promising leads for further reaction optimization. The reaction of **5** with the oxazolidinone-derived substrate **1** in the presence of Zn(NTf₂)₂ and **6** gave the addition product in good yield and good enantioselectivity when the reaction was performed at room temperature (Table 1, entry 1). In contrast, the same reaction at -30°C gave trace amounts of the alkylation product (Table 1, entry 2). In an attempt to improve reactivity and selectivity, we evaluated the use of



Scheme 1. Enantioselective protonation in Friedel–Crafts alkylations.

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Table 1: Template identification and optimization of reaction conditions.^[a]

Entry	SM	Lewis Acid	T [°C]	t	Product	Yield [%] ^[b]	ee [%] ^[c]
1	1	Zn(NTf ₂) ₂	25	2 h	7	89	83
2	1	Zn(NTf ₂) ₂	−30	16 h	7	< 10	ND
3	2	Zn(NTf ₂) ₂	25	2 h	8	98	77
4	2	Zn(NTf ₂) ₂	−30	16 h	8	14	ND
5	3	Zn(NTf ₂) ₂	25	8 h	9	36	60
6	4	Zn(NTf ₂) ₂	25	10 min	10	98	84
7	4	Zn(ClO ₄) ₂	25	1 h	10	62	90
8	4	Zn(NTf ₂) ₂	−30	1 h	10	98	93
9	4	Zn(NTf ₂) ₂	−50	16 h	10	96	93

[a] For detailed reaction conditions, see the Supporting Information; SM = starting material. [b] Yield of isolated products after purification by column chromatography. [c] Determined by HPLC on a chiral stationary phase; ND = not determined.

pyrazolidinone and N–H imide auxiliaries in the model reaction system. These auxiliaries were chosen because, unlike oxazolidinone, they have been shown to increase reactivity by minimizing A^{1,3} strain when appended to α,β -unsaturated carbonyl substrates.^[11] Pyrazolidinone substrate **2** reacted well at room temperature with Zn(NTf₂)₂/6 (Table 1, entry 3) as the chiral Lewis acid, but again gave poor reactivity at −30 °C (Table 1, entry 4). The N–H imide template **3**, which nearly eliminates the potential for A^{1,3} strain, gave surprisingly low reactivity and reduced selectivity relative to substrates **1** and **2** (Table 1, entry 5).

At this point we sought an achiral auxiliary that would minimize A^{1,3} interactions and provide enhanced reactivity under the low-temperature reaction conditions required for improved enantioselectivity. To this end, we have designed a new and easily prepared achiral isoxazolidinone^[14] template, (substrate **4**), in which incorporation of oxygen avoids A^{1,3} interactions and also provides electronic activation relative to oxazolidinone **1**. The room-temperature reaction of **4** with **5** in the presence of Zn(NTf₂)₂/6 gave improved reactivity (98 % yield in 10 min, as compared to 89 % yield in 2 h for **1**, Table 1, entry 6 vs entry 1) with comparable selectivity (84 % ee vs 83 % ee). Notably, the use of Zn(ClO₄)₂/6 as the chiral Lewis acid led to improved enantioselectivity, but lower reaction efficiency (Table 1, entry 7 vs entry 6). However, the improved reactivity of isoxazolidinone **4** enabled the Zn(NTf₂)₂/6-catalyzed reaction with **5** to proceed efficiently at lower temperatures (−30 and −50 °C), with superior enantioselectivity (93 % ee, Table 1, entries 8 and 9). These experiments constitute the first examples of successful enantioselective protonation during Friedel–Crafts alkylations.^[15] Furthermore, they demonstrate that the achiral template plays a key role in the outcome of the reaction, with respect to

reactivity and selectivity. Control experiments suggest that the reaction is under kinetic control and external proton donors such as phthalimide or succinimide had negligible impact on selectivity.^[16] We propose that intermediate **B** (Scheme 1) is the most likely proton source in these experiments.

We have evaluated the scope of the reaction, with respect to the α,β -substituent on the α,β -unsaturated imide acceptor, using the optimal conditions identified in Table 1. The results are presented in Table 2. As noted earlier, the reaction of α -methyl acrylate **4** with **5** gave the corresponding product in high yield and high enantioselectivity (Table 2, entry 1). An even higher level of enantioselectivity was obtained with an α -ethyl-substituted acceptor (Table 2, entry 2). Substrates containing functionalized α substituents were also competent acceptors, furnishing the

products in high yields and selectivities (Table 2, entries 3 and 4). A styrene derivative **14** also gave the alkylated product with high selectivity (Table 2, entry 5). Thus, the new methodology is tolerant of a variety of substituents at the α carbon with respect to chemical efficiency (68–98 % yield) as well as enantioselectivity (93–98 % ee).

The scope of the pyrrole nucleophile in the F–C alkylation/enantioselective protonation reaction was also investigated (Table 3). A variety of pyrroles were evaluated under the optimal reaction conditions using substrate **4** as the acceptor. The reaction of the parent pyrrole gave the alkylated product in excellent yield and selectivity (Table 3, entry 1). *N*-Alkyl pyrroles were even more efficient (Table 3, entries 2–5). A variety of alkyl substituents on the pyrrole

Table 2: Evaluation of the scope of the acceptor.^[a]

Entry	SM	t [h]	Product	Yield [%] ^[b]	ee [%] ^[c]
1	4	1	10	98	93
2	11	2	15	89	97
3	12	3	16	90	98
4	13	4	17	68	98
5	14	48	18	74	97

[a] For detailed reaction conditions, see the Supporting Information. TIPS = triisopropylsilyl. [b] Yield of isolated products after purification by column chromatography. [c] Determined by HPLC on a chiral stationary phase.

Table 3: Evaluation of the scope of the nucleophile.^[a]

Entry	R ¹	R ²	Nuc	t [h]	Product	Yield [%] ^[b]	ee [%] ^[c]
1	H	H	19	1	26	75	81
2	Me	H	5	1	10	98	93
3	Et	H	20	1	27	92	91
4	CH ₂ CH ₂ Br	H	21	2	28	84	90
5	Bn	H	22	3	29	84	91
6 ^[d]	Ph	H	23	16	30	70	73
7	H	Et	24	1	31	98	43
8	Me	Et	25	1	32	98	88

[a] For detailed reaction conditions, see the Supporting Information.

[b] Yield of isolated products after purification by column chromatography.

[c] Determined by HPLC on a chiral stationary phase.

[d] Reaction at room temperature.

nitrogen were tolerated and gave products in good to excellent yields with > 90% enantioselectivities. In contrast, the reaction of the less nucleophilic *N*-phenylpyrrole with **4** was less efficient and gave product **28** with lower selectivity (Table 3, entry 6). Using 2-ethyl pyrrole as the nucleophile gave the product in nearly quantitative yield, but with modest enantioselectivity (Table 3, entry 7). Gratifyingly, the reaction of 2-ethyl-*N*-methylpyrrole gave a single alkylated product in very high yield and high selectivity (Table 3, entry 8).

The absolute stereochemistry of product **10** was determined to be *S* by correlation.^[16] Molecular models of the enolate intermediates **D** and **E** suggest that the *S* absolute configuration resulted from protonation of the *Z* enolate **E** rather than *E* enolate **D** (Scheme 1). The intermediacy of the *Z* enolate **E** in turn implies that nucleophilic addition occurs on the *s*-*cis* rotamer **F**. The preferred reactivity of the *s*-*cis* over the *s*-*trans* rotamer has been observed in related systems and appears to have some generality.^[11e] While this *s*-*cis* preference is not fully understood, it appears likely to be electronic rather than steric in origin.^[17] The extension of the present methodology to different classes of nucleophiles and α,β -disubstituted acceptors is underway.

Experimental Section

General Procedure for Friedel–Crafts Alkylation/Enantioselective Protonation Reactions: A mixture of Zn(NTf₂)₂ (0.060 mmol) and Ph–dbfox ligand **6** (0.066 mmol) in CH₂Cl₂ (1 mL) was stirred at room temperature for 30 min. 4 Å molecular sieves (100 mg) were then added, followed by the α -substituted acrylate acceptor (0.20 mmol) and the pyrrole nucleophile (1.0 mmol). The reaction was monitored by ¹H NMR spectroscopy. When the reaction was complete, the reaction mixture was concentrated and purified by flash column chromatography on silica, using mixtures of hexane and ethyl acetate as the eluent.

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- [1] For a recent review on enolate protonation, see: L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653.
- [2] For examples, see: a) S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120; b) K. Ishihara, D. Nakashima, Y. Hiraiwa, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 24; c) J. Gil, M. Medio-Simon, G. Mancha, G. Asensio, *Eur. J. Org. Chem.* **2005**, 1561; d) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem.* **2007**, *119*, 7220; *Angew. Chem. Int. Ed.* **2007**, *46*, 7090; e) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246.
- [3] For examples, see: a) E. Vedejs, A. W. Kruger, N. Lee, S. T. Sakata, M. Stec, E. Suna, *J. Am. Chem. Soc.* **2000**, *122*, 4602, and references therein; b) W. Wang, M.-H. Xu, X.-S. Lei, G.-Q. Lin, *Org. Lett.* **2000**, *2*, 3773; c) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406.
- [4] Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.* **2004**, *6*, 1861.
- [5] a) K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *Angew. Chem.* **2001**, *113*, 454; *Angew. Chem. Int. Ed.* **2001**, *40*, 440; b) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641.
- [6] a) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; b) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571; c) C. G. Frost, S. D. Penrose, K. Lambshead, P. R. Raithby, J. E. Warren, R. Gleave, *Org. Lett.* **2007**, *9*, 2119; d) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159.
- [7] a) G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, **1973**; b) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199.
- [8] For a recent review on asymmetric Friedel–Crafts chemistry, see: T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903.
- [9] a) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 160; b) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780.
- [10] a) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370.
- [11] a) M. P. Sibi, N. Prabakaran, S. G. Ghorpade, C. P. Jasperse, *J. Am. Chem. Soc.* **2003**, *125*, 11796; b) M. P. Sibi, G. Petrovic, J. Zimmerman, *J. Am. Chem. Soc.* **2005**, *127*, 2390; c) M. P. Sibi, L. M. Stanley, T. Soeta, *Org. Lett.* **2007**, *9*, 1553; d) M. P. Sibi, J. B. Sausker, *J. Am. Chem. Soc.* **2002**, *124*, 984; e) M. P. Sibi, Z. Ma, K. Itoh, N. Prabakaran, C. P. Jasperse, *Org. Lett.* **2005**, *7*, 2349.
- [12] For the use of pyrroles in enantioselective Friedel–Crafts reactions, see: a) B. M. Trost, C. Muller, *J. Am. Chem. Soc.* **2008**, *130*, 2438; b) M. Abid, L. Teixeira, B. Török, *Org. Lett.* **2008**, *10*, 933; c) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; d) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029; e) G. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065.
- [13] U. Iserloh, Y. Oderaotoshi, S. Kanemasa, D. P. Curran, *Org. Synth.* **2003**, *80*, 46.
- [14] a) A. S. Reddy, M. S. Kumar, G. R. Reddy, *Tetrahedron Lett.* **2000**, *41*, 6285; b) S. Wolfe, M.-C. Wilson, M.-H. Cheng, G. V. Shustov, C. I. Akuche, *Can. J. Chem.* **2003**, *81*, 937.
- [15] Reducing the catalytic loading from the optimal 30 mol % led to lower yield, selectivity, and longer reaction time.
- [16] See the Supporting Information for details.
- [17] D. M. Birney, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 4127.