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Magnesium Coordination-Directed *N*-Selective Stereospecific Alkylation of 2-Pyridones, Carbamates, and Amides Using α-Halocarboxylic Acids

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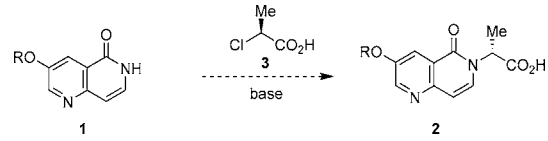
Abstract: A general inversion-stereospecific, *N*-selective alkylation of substituted 2-pyridones (and analogues), amides, and carbamates using chiral α-chloro- or bromocarboxylic acids in the presence of KO*t*-Bu (or KHMDS) and Mg(O*t*-Bu)$_2$ is reported. The resulting α-chiral carboxylic acid products were isolated by crystallization in good chemical yields and in high *ee* (>90% *ee*). Mechanistic evidence suggests that the reaction proceeds through 2-pyridone *O*-coordinated Mg carboxylate intermediates, which afford the product through an intramolecular S_N2 alkylation.

Installation of chiral centers in nonpeptide-based pharmaceuticals remains one of the most challenging aspects of process research development. Over the past few decades, the toolbox has been significantly expanded with the development of chiral auxiliary and asymmetric catalysis.[1] Nevertheless, scalable methods not requiring extra activation steps remain to be relatively few.[2] On the other hand, traditional chiral building blocks derived from renewable natural resources often can serve as a less expensive and more direct approach, and hence a greener choice. However, this approach is often underappreciated partly due to a perceived lack of structural diversity. Enantiomerically enriched α-chloro- and α-bromocarboxylic acids are commercially available, and inexpensive chiral building blocks derived from abundant amino acids.[3] In addition, recent developments in the field of organocatalysis continue to expand the availability of analogous, structurally diverse chiral synthons.[4] Here, we report a versatile *N*-selective alkylation of 2-pyridone (and analogues) using α-halocarboxylic acids *via* an unprecedented magnesium-coordinated intramolecular S_N2 mechanism.

Chiral *N*-substituted 2-pyridone carboxylic acids (and analogues) are a common structural motif present in many pharmaceutically relevant compounds and natural products.[5] Existing methods[6] often suffer from lengthy sequences, limited scope, intermediate epimerization, or low *O*/*N* chemoselectivity. Recently, we were interested in preparing a highly enantiomerically enriched naphthyridinone acid **2**, for which an *N*-selective, stereospecific alkylation using enantiomerically enriched (*S*)-2-chloropropionic acid **3** would be the most efficient route (Scheme 1).

Although direct S_N2 alkylations using **3** with simple alkoxide and phenoxide nucleophiles have been demonstrated,[7] alkylation of naphthyridinone **1** in a similar fashion presented a significant challenge due to *N*/*O* chemoselectivity issues[8] and the increased steric bulk of the nucleophile. The expected decreased reactivity of **1** presents an additional challenge since two stereodivergent reaction manifolds may be operative with electrophile **3**, namely inversion resulting from an S_N2 mechanism and retention through the intermediacy of an α-lactone.[9] In addition, a strong base such as KO-*t*Bu is capable of rapidly epimerizing the product.[10] Despite these potential pitfalls, the efficiency of this route warranted investigation. We evaluated the utility of various bases to effect the desired alkylation (Table 1, entries 1−6). The use of alkali metal *tert*-butoxides (Na or K) resulted in significant *ee* erosion and complicated side reactions. The use of a weaker base such as NaOSiMe$_3$[7d] or the low-solubility base Cs_2CO_3 did not give satisfactory results. Interestingly *N*- *vs* *O*-chemoselectivity was observed to be largely dependent on the nature of the cation where Lewis acidic Li and Mg gave exclusively the desired *N*-alkylated product, albeit in low yield due to poor reactivity.

Scheme 1. Synthetic Route for Enantioenriched *N*-Naphthyridinone Propionic Acid **2**



The high chemoselectivity of Mg(O*t*-Bu)$_2$ led us to investigate combinations where the reactive sodium amide was combined with magnesium carboxylate, with hopes to take advantage of the enhanced nucleophilicity on one hand and increased electrophilicity on the other (Table 1, entry 7). To our delight, the combination did improve the reactivity and *N*/*O* selectivity with small *ee* erosion. Remarkably, pregenerating the two species was not necessary; an all-in or even reversed combination (preforming the magnesium amide and sodium carboxylate) reaction gave similar outcomes, suggesting cation metathesis occurs rapidly under the reaction conditions. Replacing NaO*t*-Bu with KO*t*-Bu improved the reaction profile further (Table 1, entry 8). On the other hand, replacing Mg(O*t*-Bu)$_2$ with the more Lewis acidic Al(O*t*-Bu)$_3$ was detrimental in terms of reactivity (Table 1, entry 9). Further optimization of the conditions allowed for the reaction to be run more concentrated (desirable for scale-up) (Table 1, entry 10). Also the charge of bases was optimal with increases to 2 equiv of Mg(O*t*-Bu)$_2$ and 1.05 equiv of KO*t*-Bu. Finally we observed that aging the all-in mixture at 20 °C for at least 2 h provided a more consistent and faster reaction upon heating to the reaction temperature of 55 °C with >96% conversion typically observed within 7 h (Table 1, entry 11). The loss in optical purity of product verses the (*S*)-chloropropionic acid was typically less than 1.5% *ee* under these optimized conditions. It should also be noted that the dryness of the starting materials and solvent should be ensured for the high reactivity as water was found to reduce the reaction rate.[11]

The stereospecific alkylation with 2-chlorocarboxylic acid was found to be general with 2-pyridone analogues and aliphatic amides as suitable nucleophiles. In general, *N*/*O* selectivity was excellent in all cases. With a more hindered alkyl halide (Table 2, entry 5), the reaction was slower and required a higher temperature to reach high conversion. With less acidic amide substrates where KO*t*-Bu

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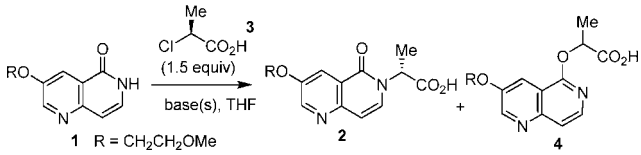
Table 1. Optimization of Direct Alkylation with (*S*)-2-Chloropropionic Acid



entry	base (equiv)	[M]	temp/time	yield (conv)[a]	N/O ratio[b]	ee loss[c]
1	KO*t*-Bu (2.5)	0.25	reflux/20 h	48% (92%)	2.6:1	>10%
2	NaO*t*-Bu (2.5)	0.25	reflux/2 h	76% (93%)	3.5:1	18%
3	$NaOSiMe_3$ (2.5)	0.25	reflux/24 h	53% (87%)	3.5:1	10%
4	Cs_2CO_3 (5.0)	0.25	60 °C/3.5 h	79% (>99%)	5.7:1	6%
5	LiO*t*-Bu (2.5)	0.25	reflux/20 h	62% (67%)	>100:1	8%
6	$Mg(Ot\text{-}Bu)_2$ (2.5)	0.25	reflux/20 h	38% (37%)	>100:1	13%
7	NaO*t*-Bu (1.0) $Mg(Ot\text{-}Bu)_2$ (1.5)	0.25	reflux/20 h	73% (81%)	>100:1	4%
8	KO*t*-Bu (1.0) $Mg(Ot\text{-}Bu)_2$ (1.5)	0.25	reflux/20 h	82% (85%)	>100:1	2%
9	KO*t*-Bu (1.0) $Al(Ot\text{-}Bu)_3$ (1.5)	0.25	reflux/20 h	16%(16%)	>100:1	N.A.
10	KO*t*-Bu (1.0) $Mg(Ot\text{-}Bu)_2$ (2.0)	1.0	reflux/20 h	89% (92%)	>100:1	2.5%
11	KO*t*-Bu (1.05) $Mg(Ot\text{-}Bu)_2$ (2.0)	1.0	55 °C/7 h	95% (96.7%)	>100:1	<1.5%[d]

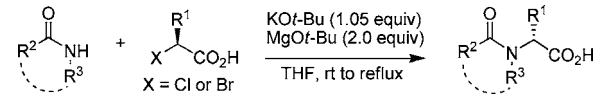
[a] LC assay yield and conversion; reaction conditions: **1** (1 equiv, 0.6−2 mmol scale), **3** (1.5 equiv), and base(s) in dry THF. [b] LC signal ratio at the wavelength of 254 nm, molar ratio = 2.3 × LC ratio. [c] Starting material 92−98% *ee*, *ee* loss = *ee* (**3**) − *ee* (**2**). [d] The reaction was formed on a 15 mmol scale; aged all-in reaction mixture for 2.5 h before heating to 55 °C (batch temperature).

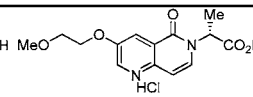
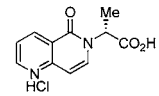
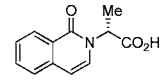
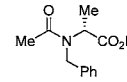
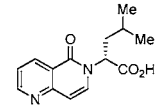
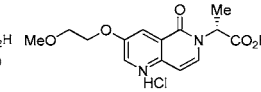
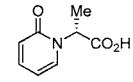
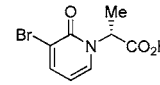
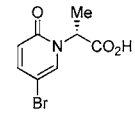
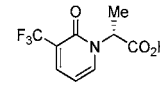
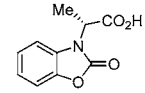
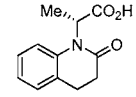
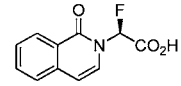
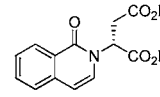
is no longer sufficient for complete deprotonation (Table 2, entry 4), KHMDS was used instead to improve the reactivity. The reaction scope was further extended to α-bromocarboxylic acids which are equally accessible with high enantiomeric purity. Not surprisingly the α-bromocarboxylic acids were more reactive, allowing good conversion at lower temperatures (≤35 °C) and affording the crude product with complete preservation of enantiomeric purity and high *N*/*O* selectivity (Table 2, entry 6). The reaction is general with respect to the nucleophile as well, such as a variety of substituted 2-pyridones (Table 2, entries 7−10), carbamates (Table 2, entry 11), and cyclic amides (Table 2, entry 12). It is of particular interest that a highly enantioenriched α-fluoro acid product can be obtained from nonracemic α-fluoro-α-bromoacetic acid (Table 2, entry 13).[12] As expected 2-bromosuccinic acid was not a competent electrophile in this reaction, presumably due to the formation of an unreactive cyclic magnesium species (Table 2, entry 14). It is also noteworthy that, in all cases, the alkylated products were isolated and purified by crystallization, typically with an upgrade in enantiomeric purity.

The observed synergy between magnesium and potassium bases with respect to reaction rate and chemoselectivity suggested a unique mechanism for this reaction. X-ray crystallography confirmed inversion of the absolute stereochemistry for both α-chloro- and α-bromo acid substrates, consistent with phenol alkylation chemistry.[7e] A competition experiment between the acid **3** and methyl ester **5** revealed that the former was at least two orders of magnitude more reactive (Scheme 2). Such a difference is counterintuitive since the significant anionic character of the metal carboxylate would only decrease its reactivity based on an S_N2 model.[13] A plausible explanation is that the magnesium carboxylate is coordinated to the naphthyridinone anion to give an intramolecular S_N2 with a significant increase of the *effective molarity* of the alkylation agent.[14] A rate order experiment would have been the most direct method to differentiate an inter- or intramolecular S_N2 mechanism; however, heterogeneity of the reaction mixture complicated this matter.

To differentiate whether magnesium serves to bring the electrophile and nucleophile into proximity or to merely activate the C−Cl bond

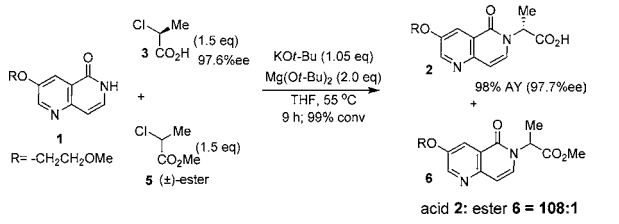
Table 2. Scope of the Direct *N*-Alkylation



entry	reagent	isolated product[a]	yield[b]	ee[c]
1	 (97.6%ee)		92% (97%)	97% (97%)
2	 (97.6%ee)		89% (95%)	98% (94%)
3	 (97.6%ee)		94% (95%)	94% (94%)
4	 (97.6%ee)		79%[d] (80%)	86% (86%)
5			73% (80%)	95% (90%)
6	 (94.3%ee)		93% (96%)	95% (94%)
7	 (94.3%ee)		74% (87%)	97%
8	 (94.3%ee)		80% (82%)	96% (95%)
9	 (94.3%ee)		88% (91%)	96%
10	 (94.3%ee)		87% (90%)	94%
11	 (94.3%ee)		87% (93%)	96%
12	 (94.3%ee)		77% (85%)	>99% (93%)
13	 (99%ee)		80%	94%
14			N.R.[d]	N.A.

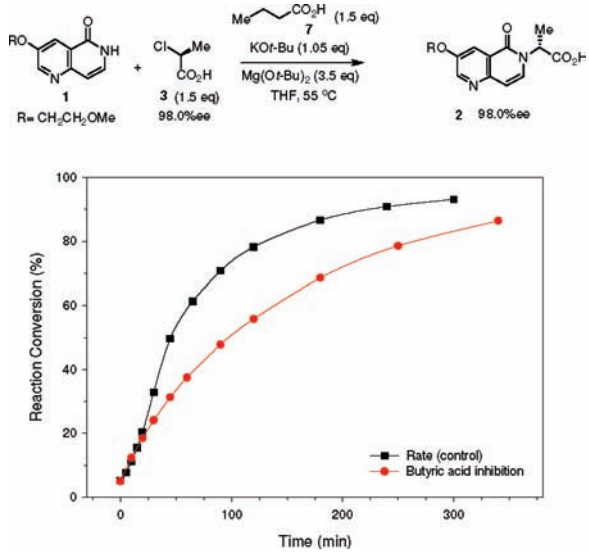
[a] Reaction conditions: Combined nucleophile (1 equiv, 3−15 mmol scale), halide (1.5 equiv), KO*t*-Bu (1.05 equiv), and $Mg(Ot\text{-}Bu)_2$ (2.0 equiv) in dry THF. The product was isolated as the form indicated in the table. [b] Isolated yield by salt formation/crystallization; crude assay yield in the parentheses. [c] *Ee* assayed by chiral HPLC; crude *ee* assay results in the parentheses. [d] KHMDS is used to deprotonate the amide, and Mg carboxylate was pregenerated and *t*-BuOH was removed. [d] $Mg(Ot\text{-}Bu)_2$ (3.0 equiv) charged.

Scheme 2. Competition between Acid and Ester



by intramolecular Mg−Cl coordination (as intermediate **8** illustrated in Scheme 3), butyric acid (1.5 equiv) was charged along with additional equivalents of $Mg(Ot\text{-}Bu)_2$ (Chart 1) to observe its effect on the kinetic profile. The fact that *in situ* generated magnesium butyrate slowed down the reaction compared to the control experiment implies that the latter is a less likely scenario. The slower rate is likely due to magnesium butyrate competitively binding the naphthyridinone anion.

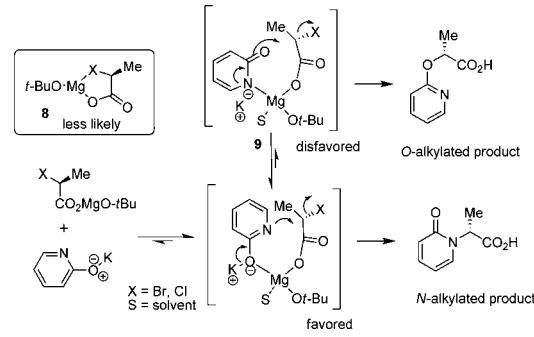
Chart 1. Kinetic Comparison between Added Butyric Acid and Control



Based on these experiments, a simplistic mechanism can be proposed in which the alkylation reaction takes place through magnesium carboxylate coordination at the oxygen of the potassium amide, resulting in an intramolecular 7-*exo-tet* alkylation (Scheme 3).[15] It is also likely that the congested magnesium metal center with multiple ligands (typically six coordination) could exert an additional Thorpe−Ingold effect to further enhance the reactivity.[16] This Mg tethered complex **9** is reminiscent of Stork's Mg-templated intramolecular Diels−Alder reaction.[17] The oxaphilic nature of magnesium also explains the exclusive selectivity of *N*-alkylation verses *O*-alkylation.[18]

In summary, we have found a highly efficient synthetic method for the stereoselective *N*-alkylation of 2-pyridones, amides, and carbamates with a nonracemic α-chloro- or α-bromocarboxylic acid using a combination of a potassium and magnesium base. The reaction gives inversion of stereochemistry with high fidelity to afford a variety of highly valuable, enantiomerically enriched *N*-heterocyclic α-carboxylic acids in one step. Experimental evidence suggests that the intramolecular S_N2 of an *O*-coordinated magnesium carboxylate amide is likely responsible for the reactivity and selectivity.

Scheme 3. Proposed Mechanism



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Supporting Information Available: Complete ref 5b and 5e, additional supporting data, complete experimental procedures, characterization data, X-ray single crystal data, and chromatographic analyses of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Product **2** completely racemizes with excess MO*t*-Bu (M = Li, Na, K) in THF at 60 °C.
(11) The crude all-in reaction mixture was assayed using Karl Fischer titrator. An equivalent of <0.2 wt% H_2O is necessary for this high reactivity.
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