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Lanthanide and asymmetric catalyzed syntheses of sterically hindered 4-isoxazolyl-1,4-dihydropyridines and 4-isoxazolyl-quinolones

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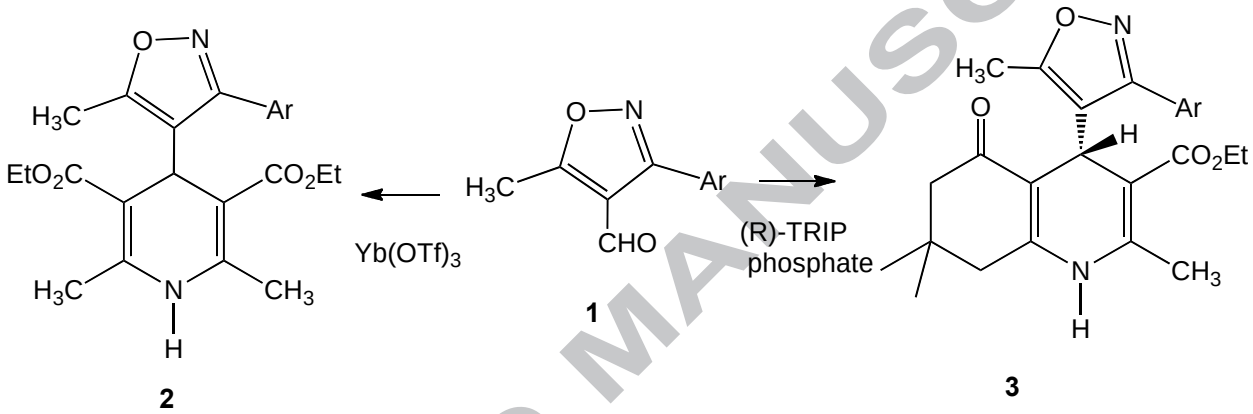
Multi-component organic cyclizations,[1] exemplified by the Hantzsch pyridine synthesis have been know for over a century.[2] The concept of scaffolds and scaffold hopping in medicinal chemistry is much more recent, however, the number of potentially useful applications of scaffolds is arithmetically increased by their judicious combination, and especially valuable are those combinations which are attainable by efficient stereoselective methodology.

Interest in the usefulness of Hantzsch esters was exponentially enhanced by the discovery that specific 4-aryldihydropyridines (DHPs) possessed robust biological activity as calcium channel antagonists, and thus are useful as antihypertensive medicines.[3] In many cases, there is a pronounced enantioselectivity of action,[4] yet as often observed the agents in general medical practice have been obtained by chromatographic or classical resolution. The corresponding 4-aryl quinolones have been found to have useful activity as inhibitors of TGFβ Signaling,[5,6] and as agents which reduce cellular tau levels which represents an important target in Alzheimer's disease,[7,8] and are the current subject of intensive pre-clinical development. Early advances in stoichiometric adjuvant asymmetric synthesis of chiral DHPs were accomplished first by Meyers

and Natale,[9] and later by Enders,[10] and Dondoni.[11] The critical breakthrough to catalytic multi-component asymmetric DHP synthesis was achieved initially by Gong,[12] and extended to quinolones by Gestwicki.[7] We herein report, to the best of our knowledge, the first facile preparation of the most sterically hindered 4-isoxazolyl-1,4-dihydropyridines to date, the first examples of 4-isoxazolyl-quinolones, as well as their highly stereoselective organocatalytic asymmetric synthesis.



Scheme 1. Lanthanide catalyzed synthesis of sterically hindered 3-aryl-Isoxazolyl-Dihydropyridines **2**, and asymmetric organocatalysis of dihydroquinolones **3.**

The Isoxazolyl-dihydropyridines are characterized by their complex conformational dynamics,[13] which we have demonstrated can lead to divergent structure activity relationships (SAR) for different biomolecular targets.[14,15] In previous studies we observed that increasing the size of substituents on the isoxazole lead to vanishingly low yields, even under forcing conditions.[16] As an example, naphthyl groups appended to isoxazoles, even separated by an ethylene spacer, produced typical single digit yields in the Hantzsch synthesis, even under elevated pressure. Previous reports on the use of lanthanide catalysts are noteworthy for their relatively mild reaction conditions, and we sought to test the scope and limitations of this promising methodology.

The Ytterbium catalyzed[16] method produced moderate to good yields of IDHPs unavailable using standard methods. The single crystal x-ray diffractometry (sc-xrd) of **2a** and **2b** illustrates the steric crowding of the C-3 isoxazole substituent. Characteristic of IDHPs, in the unit cell, intermolecular hydrogen bonding is observed between the isoxazole ring N and the DHP N-H. In the anthryl example, **2c**, significant anisotropy is observed in the ^{1}H NMR for *both* the C-2 and C-6 methyl groups of the DHP moiety, consistent with an analogous conformation in solution.

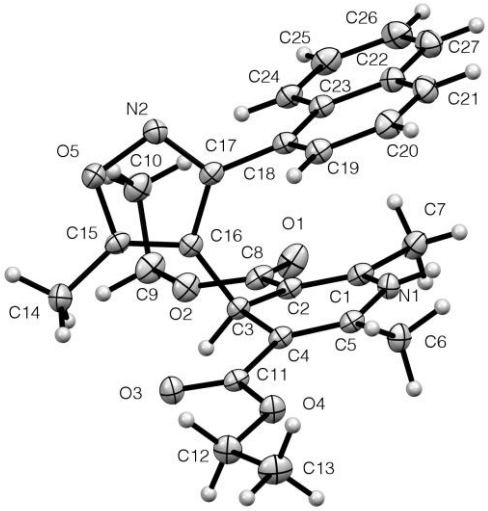
Single crystal x-ray diffractometery and solid state conformation.

The Isoxazolyl-quinolone was crystallized and its structure determined by x-ray diffractometry. The heterocyclic axis at the quinolone C-4 is oriented *O-endo*, that is, with the isoxazolyl oxygen towards the dihydropyridine moiety, and the 3'-aryl *exo* to the quinolone. The Quinolone 3-ester adopts a *synperiplanar* conformation, the quinolone locks the C-5 ketone in the *antiperiplanar* conformer. In the unit cell, there is an intermolecular hydrogen bond between the quinolone N-1 hydrogen, and the quinolone ring carbonyl oxygen.

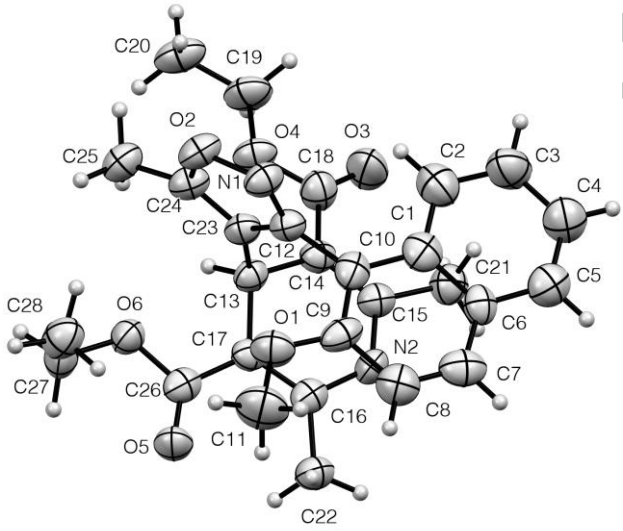
Table 1. Lanthanide catalyzed synthesis of sterically hindered IDHPs **2a-i.**

Entry	Ar	% yield	HRMS calc'd	Found
2a	1'-Naphthyl	64.04	501.2026	501.2019
2b	1'-(2'-methoxy-Naphthyl)	50.21	491.2182	491.2205
2c	9'-Anthryl	41.98	511.2233	511.2228
2d	3,4-Bis-benzyloxy-phenyl	67.95	469.1975	469.1990
2e	3-Phenoxy- phenyl	60.98	501.2026	501.2019
2f	4-Methoxy- phenyl	60.96	441.2026	441.2057
2g	2,4-Dimethoxy- phenyl	63.98	623.2757	623.2709
2h	3,4-Dimethoxy- phenyl	53.19	623.2757	623.2807
2i	4-Biphenyl	46.23	487.2233	487.2256

A



B



C

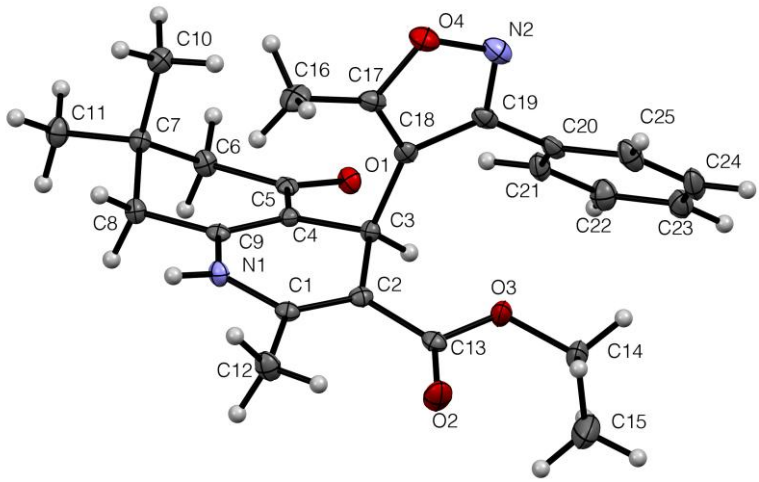


Figure 1. 50% probability ellipsoids ORTEPs of (A) Naphthyl-**2a**. R = 5.1%. (B) Methoxy-Naphthyl-**2b**. R= 9%. **(C)** IQ (±)-**3a**, R = 5.2%.

The asymmetric synthesis was performed according to Gestwicki,[6] from the isoxazole aldehydes using the organocatalysis of BINOL phosphates as pioneered by Gong. Chemical yields were moderate to good, and optical purities as established by HPLC-CSP were excellent (>90% e.e.). Absolute configurations were assigned by analogy to the work of Schade,[7] who established the absolute configuration of the (+) enantiomer as *(R)*- by single crystal x-ray diffractometry. The quinolone absolute configuration is probably driven by the relative reactivity rates of ketoester verses cyclic 1,3-diketone, and therefore arises from initial Knovenagel condensation by the ketoester, followed by Michael addition of the diketone. In contrast, the IDHP in Entry **2j**, the Knovenagel product was preformed with the triazole, followed by condensation with the ketoester. Therefore, that the absolute configuration of the entries in **Table 2** are all (-), (S)- is fortuitous. We would not expect the corresponding multi-component synthesis of IDHPs analogous to **2j** to proceed with significant stereoselectivity, unless the initial Knovenagel adduct was similarly preformed.

Table 2. Asymmetric organocatalytic synthesis of IDHP **2j** and 4-isoxazolyl-Quinolones, **3.** All examples gave optical purities of >90% e.e by HPLC-CSP (Supporting data).

Entry	Ar	R	Catalyst	Yield	$[\alpha]_D$
RS-**3a**	-Ph	$-CH_2CH_3$	$Yb(OTf)_3$	30.25	
(-)-**3a**			(R)-TRIP	25.92	-11.2
RS-**3b**	-*o*-Br-Ph	$-CH_2CH_3$	$Yb(OTf)_3$	71.60	
(-)-**3b**			(R)-TRIP	64.35	-13.5
RS-**3c**	-*m*-Br-Ph	$-CH_2CH_3$	$Yb(OTf)_3$	62.07	
(-)-**3c**			(R)-TRIP	60.40	-2.36
RS-**3d**	-*p*-Br-Ph	$-CH_2CH_3$	$Yb(OTf)_3$	67.19	
(-)-**3d**			(R)-TRIP	65.34	-0.032
RS-**2j**	-*p*-Br-Ph	-4-CH_2(N-phenethyl)triazole	$Yb(OTf)_3$	31.56	
(-)-**2j**			(R)-TRIP	21.32	-2.68

We are intrigued by the potential of the hindered 4-isoxazole dihydropyridines and 4-isoxazolyl-quinolones for theranostic applications,[18] and look forward to detailed study of their conformational dynamics and bioactivity. We will report on our progress in due course.

Supplementary Material

Full experimental details and characterization for all new compounds. Crystal structure determination, atomic coordinates and hydrogen-bond geometry for **2a**, **2b**, and RS-**3a**, including unit cells. SYBYL transition state modeling of the organocatalytic asymmetric synthesis.

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