

Accepted Manuscript

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PII: S0040-4039(15)30452-4
DOI: <http://dx.doi.org/10.1016/j.tetlet.2015.12.038>
Reference: TETL 47085

To appear in: *Tetrahedron Letters*

Received Date: 23 November 2015
Accepted Date: 8 December 2015



Please cite this article as: Steiger, S.A., Li, C., Campana, C.F., Natale, N.R., Lanthanide and asymmetric catalyzed syntheses of sterically hindered 4-isoxazolyl-1,4-dihydropyridines and 4-isoxazolyl-quinolones, *Tetrahedron Letters* (2015), doi: <http://dx.doi.org/10.1016/j.tetlet.2015.12.038>

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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 known 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 TGF β 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

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