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The catalytic asymmetric addition of alkyl- and aryl-zinc reagents to an isoxazole aldehyde

Jared K. Nelson [a], Brendan Twamley [a], Trinidad J. Villalobos [a], Nicholas R. Natale [a,b,*]

[a] Department of Chemistry, University of Idaho, Moscow, ID 83844-2343, USA
[b] COBRE Center for Structural and Functional Neuroscience, The University of Montana, Missoula, MT 59812, USA

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ABSTRACT

Nucleophilic addition of alkyl- and aryl-zinc reagents to a C(4) functionalized isoxazolyl aldehyde proceeded effectively with high enantioselectivity (85–94% ee). The amino alcohol catalyst (*S*)-2-piperidinyl-1,1,2-triphenyl ethanol (**10**) afforded the (*R*)-product **2b**, as established by X-ray crystallography.

Functionalized isoxazoles represent an extremely important class of compounds in the synthesis of therapeutically relevant molecules.[1] The recent report of Myers on the asymmetric addition of zinc reagents to an isoxazole aldehyde,[2] prompts this description of our own studies on an analogous C-4 functionalized system.[3] Since the landmark report of the selective glutamate receptor ligand AMPA (Chart 1),[4] the Krogsgaard-Larsen group has continued to uncover groundbreaking sub-type selectivity, exemplified by the recent observation of GluR1 selectivity of the 2-Benzyl-tetrazole (2-Bn-Tet) analog of AMPA.[5,6] In order to expand upon our previously reported catalytic asymmetric synthesis of isoxazole containing glutamate analogs,[7–9] we came to examine the nature of asymmetric addition of carbon-based nucleophiles to isoxazolyl aldehyde **1** for the synthesis of novel ACPA analogues, **3**.

Numerous methods exist for the nucleophilic addition of alkyl and aryl groups to aldehydes.[10–13] The use of zinc-based reagents was chosen based on (1) The abundance of chiral catalysts which afford the products in high yield and high enantiomeric excesses (ees); (2) the availability of a wide variety of alkyl and aryl substituents on zinc (either commercially, or via a single synthetic step); and (3) the rate of the uncatalyzed (racemic) reaction is most often near zero in the absence of a catalyst, theoretically leading to very high ees (Fig. 1).

Results from alkyl zinc additions to isoxazolyl aldehyde **1** are summarized in Table 1. The proof of concept for this series of reactions was initially examined with Et_2Zn as nucleophile and a BINOL/Ti(O*i*Pr)$_4$ co-catalysts system developed by Walsh.[10] This system was chosen due to the wide variety of functional groups tolerated as well as the consistently high yields and high ees of products formed. Unfortunately, repeated attempts at nucleophilic addition to **1** using this method failed completely. The product from aqueous workup following the reaction appears to have been produced by deprotection of the acetal and reduction of the aldehyde to the alcohol to give **4**, as shown in Scheme 1.

The next method we employed utilized a BINOL derivative **7** and a bulky diimine **9** as cocatalysts for the nucleophilic addition (Table 1, entry 4). This method succeeded in that it provided the product in 80% yield. However, the product mixture was racemic.

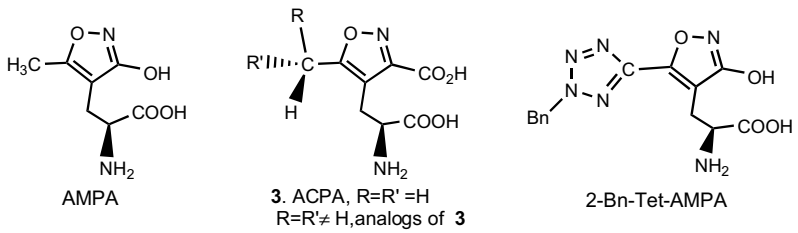

Chart 1. Isoxazole ionotropic glutamate receptor ligands.

* Corresponding author. Tel.: +1 406 243 4132; fax: +1 406 243 5228.
E-mail address: Nicholas.natale@umontana.edu (N. R. Natale).

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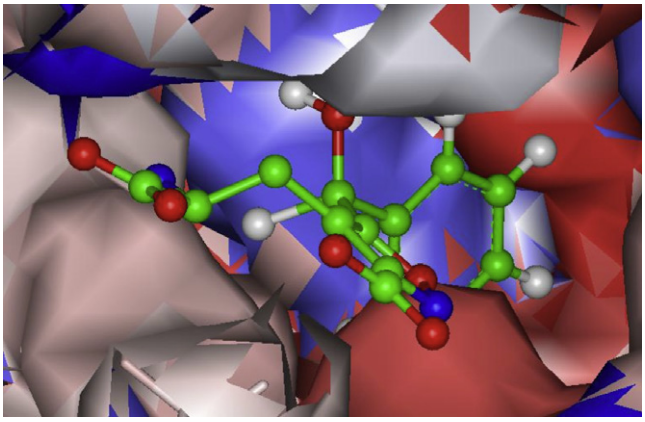
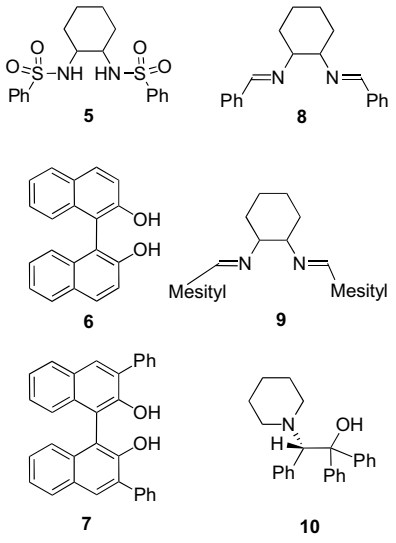


Figure 1. ACPA analog 3 (R = Ph, R′ = OH) docked into the GluR2 binding domain using INSIGHT II. Synthesis of **3** requires efficient access to chiral intermediates **2**.

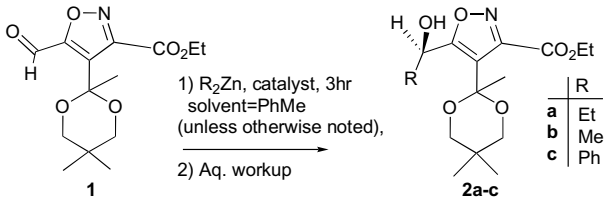
A literature search for other methods presented the amino alcohol **10**, which functioned exceedingly well to give the alcohol **2** in 96% yield and up to 93% ee at only 6 mol % catalyst (Table 1, entry 5).



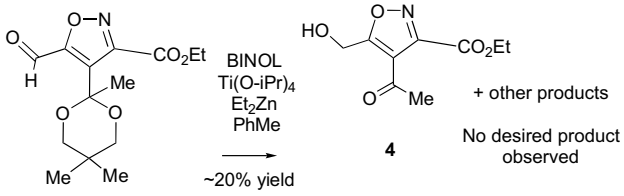
With proof of concept in hand, **10** was utilized as catalyst in the nucleophilic addition of dimethyl zinc to the aldehyde **1**. Unfortunately, with 6 mol % catalyst, the product **2b** was formed in only 67–72% ee and 69% yield. Benzene as solvent resulted in an even worse outcome with only 45% ee, and approximately the same yield as in toluene. Increasing the catalyst loading in toluene to 10 mol % improved the ee to 85% and the yield to 94% (Table 1, entry 11). Subsequent increases in catalyst loading actually resulted in a decrease in %ee and concomitant decrease in yield. With half an equivalent of the catalyst, the alcohol had dropped to 78% ee and the yield was a paltry 69%. This plateau around 80% ee may be due to the formation of an inactive dimeric catalyst in equilibrium with the active monomeric ethyl zinc alkoxide as noted by Lledos and coworkers.[14] The use of hexanes with 15 mol % catalyst (Table 1, entry 15) provided an increase in ee for the product (85%) relative to the same conditions in toluene (81%), however, the yield was slightly lower, and reactants were not entirely soluble in hexanes.

We established the absolute configuration of the resultant alcohol by X-ray crystallography. The condensation of *p*-Cl-phenylhydrazine with the ketone **11** resulted in X-ray quality crystals of pyridazinone **13** shown in Scheme 2. X-ray diffraction with

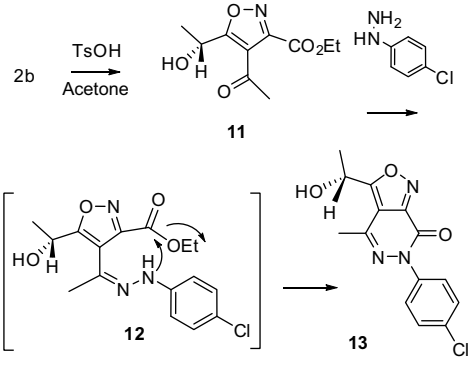
Table 1
Asymmetric nucleophilic addition of dialkylzinc reagents to aldehyde **1**



Entry	R group	Catalyst (name, mol %)	Yield	%ee
1	Et	None	0	—
2		$Ti(OiPr)_4$, **5**, 2 mol %	0	—
3		$Ti(OiPr)_4$, **5**, 10 mol %	0	—
4		**7**, 10 mol %, **9**, 10 mol %	80	0
5		**10**, 6 mol %	96	91–93
6	Me	**6**, 10 mol %	60	ND
7		**6**, 10 mol %, **8**, 10 mol %	90	ND
8		**6**, 10 mol %, **9**, 10 mol %	97	ND
9		**10**, 6 mol %, solvent = PhH	72	45
10		**10**, 6 mol %	69	67–72
11		**10**, 10 mol %	94	85
12		**10**, 15 mol %	89	81
13		**10**, 20 mol %	70	81
14		**10**, 50 mol %	69	78
15		**10**, 15 mol %, solvent = hexanes	85	85



Scheme 1. Lewis acid promoted acetal deprotection and reduction.



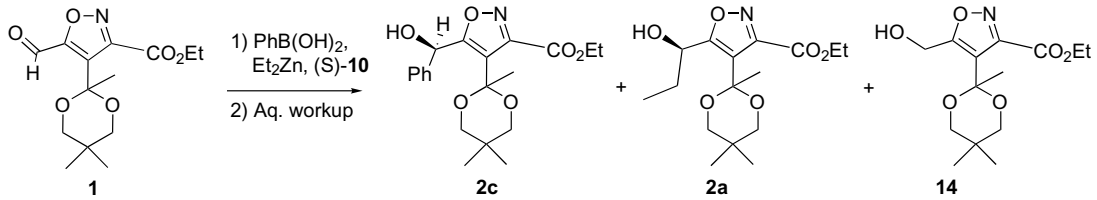
Scheme 2. Isoxazole[3,4-*d*]pyridazinone for X-ray analysis.

anomalous scattering of crystals of **13** proved that use of the (*S*)-catalyst **10** afforded the alcohol **2b** with an absolute configuration of *R*. The details of the structure determination, and crystallographic information files are provided in the Supplementary data.

The next target in this series involved the asymmetric transfer of a phenyl group to aldehyde **1**, the results of which are summarized in Table 2. The use of pure Ph_2Zn is typically not very attractive due to the high reactivity of the Zn reagent, even in the absence of a catalyst, thus resulting in a racemic mixture. However, the use of Ph_2Zn in this case (Table 2, entry 1) actually resulted in *no desired product* formed, racemic or otherwise.

Rudolph et al.[16] showed that premixing of 0.65 equiv Ph_2Zn and 1.30 equiv Et_2Zn—to give PhZnEt—highly efficiently and stereo-

Table 2
Phenyl zinc transmetalation and asymmetric addition to aldehyde **1**



Entry	Ph_2Zn (equiv)	Et_2Zn (equiv)	**2c**[a]	**2a**	**14**	%ee
1	2.0	0	0	0	0	NA
2	0.64	1.32	15	77	8	
	$PhB(OH)_2$(equiv)					
3	2.4	7.2	60(50)	10	30	90
4[b]	2.4	7.2	70	20	10	94
5	1	3	33	33	33	
6[c]	2.4	7.2	67(48)	17	16	92

[a] Isolated yields in parentheses.
[b] Inverse addition of reagents.
[c] Prepared with NEAT Et_2Zn.

selectively transfers a phenyl to various benzaldehydes. In our case, this experiment resulted in a small amount of the desired alcohol **2c**, though (quite surprisingly) ethyl transfer to produce **2a** was dominant. A small amount of alcohol **14** was also formed, presumably by reduction of aldehyde **1**. This competing pathway is commonly observed in other organometallic reactions, proceeding via hydride transfer from metals containing β-hydrogens.[17]

A method developed by Bolm and Rudolph[18] utilized phenylboronic acid in transmetallation. With 2.4 equiv $PhB(OH)_2$ and 7.2 equiv Et_2Zn a boron-to-zinc ex-change takes place generating PhZnEt in situ. They found that a threefold excess of Et_2Zn relative to $PhB(OH)_2$ was optimal for complete exchange to occur. When we attempted to add aldehyde **1** to this Zn solution containing amino alcohol catalyst **10**, the desired alcohol **2c** *was* formed, though significant amounts of ethyl addition (**2b**) and reduction (**14**) were observed as well (Table 2, entry 3). Inverse addition (adding Zn solution to the catalyst/aldehyde solution), resulted in an increase in the relative amount of **2c** observed (Table 2, entry 4), with a significantly lower occurrence of the reduction product, albeit with an increase in ethyl adduct formed as well.

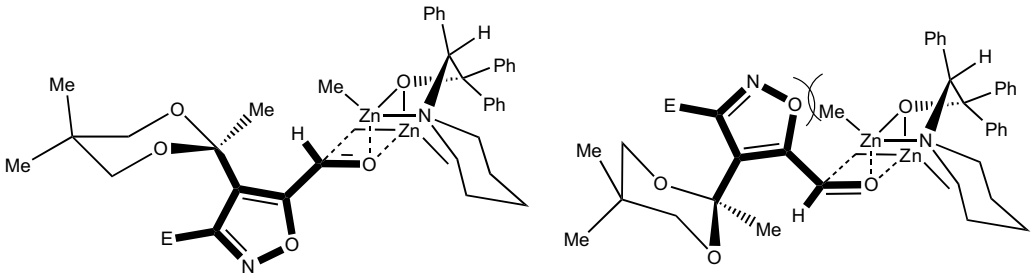
Decreasing the total amount of zinc and boron reagents to 1 equiv $PhB(OH)_2$ and 3 equiv Et_2Zn was found to destroy chemoselectivity (Table 2, entry 5), resulting in equimolar amounts of **2c**, **2a**, and **14**.

Finally, it has been shown[18] that employing *neat* Et_2Zn along with $PhB(OH)_2$ could result in improved yield of the phenyl adduct. However, our results indicate that the reaction proceeded very similarly to that in which a solution of Et_2Zn was used. The phenyl adduct **2c** was isolated in a yield of 48% (Table 2, entry 6), with a ratio of 67:17:16 for **2c**:**2a**:**14**, respectively (by ^1H NMR). The ee of the desired product was again excellent, at 92%.

These results led us to ponder the transition state of the asymmetric alkylation. The absolute stereochemistry of our observed nucleophilic addition to **1** is consistent with the model reported by Verdaguer for dinuclear zinc catalysts.[15,26] In contrast, the recent report by Myers utilized stoichiometric Oppolzer's reagent[25] on his C-4 unsubstituted isoxazole,[2] which featured a reasonable *lithium O*-isoxazole ring chelate to rationalize the observed difference in absolute stereochemistry. Such metal to O-ring and N-ring[19] interactions are among the two most commonly observed coordination modes in isoxazole coordination chemistry.[20–22] Furthermore, coordination has played a central aspect as rationale for our own isoxazole lateral metalation chemistry,[23] if not a fundamental role in the design of successful asymmetric syntheses.[24] Therefore, we conclude that (1) the sterically encumbered C-4 acetal function and (2) the absence of lithium play important roles in disrupting potential isoxazole O-ring coordination, as illustrated in Scheme 3.

When applying the transition state model noted by Verdaguer and coworkers,[15] to our system, this decrease in enantioselectivity for Me_2Zn addition relative to Et_2Zn can be explained as shown in Scheme 3. The transition state may be organized by steric interactions between the isoxazole ring and one of the methyls of dimethyl zinc. The major enantiomer would then be formed when the isoxazole ring was oriented *away* from the methyl group, as this should be the lower energy conformation (Fig. 2).

Therefore, one would expect that larger alkyl groups on zinc would direct the aldehyde more effectively, resulting in a higher



Scheme 3. Transition state model for asymmetric addition to isoxazole aldehyde **1**.

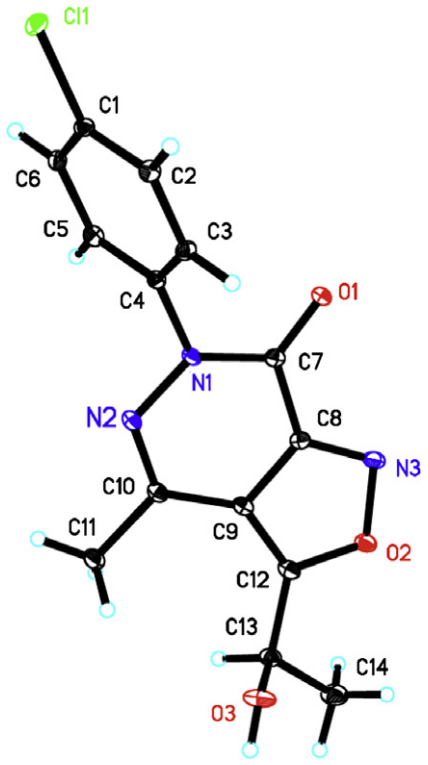


Figure 2. Molecular structure of (*R*)-**13** (thermal displacement 30%).

ee for the product. This is in fact observed as diethyl zinc adds to aldehydes with much greater enantioselectivity than dimethyl zinc.

This observation that the phenyl transfer proceeds with higher enantioselectivity is as expected from the proposed transition state model. A phenyl (or ethyl) group on zinc is sufficient to direct the isoxazole away from the zinc-catalyst complex, resulting in a greater difference in activation energies for the two possible orientations of the aldehyde in the transition state.

In summary, amino alcohol **10** has been used to add alkyl and aryl substituents to isoxazolyl aldehyde **1** in good to excellent yields and enantioselectivities, and intermediates **2** can be brought forward to ACPA analogs (**3**, R = OMe, R′ = Me, Supplementary data).[7] Synthesis of additional chiral ACPA analogues is underway, and our progress in the application of our chemistry towards the understanding of the structure–activity relationships of ligands for glutamate receptors and transporters will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data for all new compounds, and crystallographic information files (CIF) for **13**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.169.

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