**A directed enolization strategy enables the byproduct free construction of contiguous stereocenters en route to complex amino acids**

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**Abstract**

The byproduct free and stereocontrolled assembly of challenging β-substituted α-amino acids is described via Ir-catalyzed α-alkylation of glycine derivatives with non-polarized alkenes. Mechanistic studies indicate that a geometrically defined Ir-enolate is generated via NH metallation of the glycine precursor in advance of soft enolization. C-C bond formation with the alkene then occurs via a bimetallic pathway. The method is completely branch selective, highly diastereoselective and highly enantioselective. The study offers a unique approach to the direct stereocontrolled α‑alkylation of carbonyl compounds, and provides a broader framework for the stereocontrolled assembly of challenging contiguous stereocenters.

**Summary Paragraph**

Homochiral α-amino acids are widely used in pharmaceutical design, as key subunits in chiral catalyst synthesis, or as building blocks in synthetic biology. Many synthetic methods have been developed to access rare or unnatural variants by controlling the installation of the α-stereocenter.[[1]](#endnote-1),[[2]](#endnote-2),[[3]](#endnote-3),[[4]](#endnote-4),[[5]](#endnote-5),[[6]](#endnote-6),[[7]](#endnote-7) By contrast, and despite their importance,[[8]](#endnote-8),[[9]](#endnote-9)[[10]](#endnote-10) α-amino acids possessing β-stereocenters are much harder to synthesize.[[11]](#endnote-11),[[12]](#endnote-12),[[13]](#endnote-13),[[14]](#endnote-14) Here, we demonstrate an iridium-catalyzed protocol that allows the direct up-conversion of simple alkenes and glycine derivatives to give β-substituted α-amino acids with exceptional levels of regio- and stereocontrol. Our method exploits the native directing ability of a glycine-derived N-H unit to facilitate Ir-catalyzed enolization of the adjacent carbonyl. The resulting stereodefined enolate cross-couples with a styrene or α-olefin to install two contiguous stereocenters. The process offers very high levels of regio- and stereocontrol and occurs with complete atom economy. In broader terms, our reaction design offers a unique directing group-controlled strategy for the direct stereocontrolled α-alkylation of carbonyl compounds, [[15]](#endnote-15) and provides a powerful approach for the synthesis of challenging contiguous stereocenters.[[16]](#endnote-16)

**Main Text**

**Introduction:** Amino acids are arguably the most valuable homochiral building blocks available to synthetic chemists. This has stimulated the development of a variety of methods to access rare or unnatural variants, focussing predominantly on control of the α‑stereocenter.1 Exemplar catalytic asymmetric methods include Strecker reactions,2 phase-transfer-catalyzed alkylations of glycine imines,3 alkene hydrogenations,4 cross-couplings,5 and conjugate additions.6,7 Although highly effective, these approaches are not generally suitable for accessing amino acids possessing β-stereocenters (Scheme 1A). Substitution at this position has important ramifications on, for example, the three-dimensional structure of a derived peptide,8,9 or the physiochemical properties of a downstream product. As testament to this, a variety of biosynthetic processes are known that allow the β-functionalization of canonical amino acids.9,10 A handful of catalytic asymmetric methods have emerged that allow the synthesis of certain β-stereogenic α-amino acids. These include, biocatalytic dynamic kinetic resolutions,11 diastereoselective C-H arylations,12 asymmetric hydrogenations,13 and stereoretentive cross-couplings.14 These important approaches each have their own limitations and are non-trivial, requiring, for example, a preassembled framework, and/or preinstalled homochirality and/or prefunctionalized reaction partners.

We questioned whether an alternative and more convergent approach could be achieved by the *direct* and stereocontrolled C-H alkylation of a glycine-based precursor (Scheme 1B). In particular, we targeted a process where the new C-C bond and the two stereocenters are established in a single operation. In essence, this requires the invention of a catalytic method that allows the enantio- and diastereoselective *direct* (i.e. stoichiometric base‑free) intermolecular α-alkylation of carbonyl compounds. For systems that lack additional strong acidifying groups,3 this area has proven to be exceptionally challenging,15,[[17]](#endnote-17) such that auxiliary-based approaches are still dominant in target directed synthesis (Scheme 1C, Eqn 1).[[18]](#endnote-18),[[19]](#endnote-19) Asymmetric ketone α-alkylation can be achieved from lithium enolates using catalytic quantities of a chiral amine ligand (Scheme 1C, Eqn 2).[[20]](#endnote-20)Other catalytic enantioselective methods have emerged, but these are not usually direct, relying either on the preformation of an enolate or enolate equivalent,[[21]](#endnote-21),[[22]](#endnote-22),[[23]](#endnote-23) or the preinstallation of sacrificial functionality.[[24]](#endnote-24) In a key advance, MacMillan developed a tricatalytic system that promotes the *direct* linear selective α-alkylation of aldehydes (Scheme 1C, Eqn 3).[[25]](#endnote-25) This process is also significant because it harnesses readily available non-activated alkenes as alkylating agents for enantioselective α-functionalization reactions.[[26]](#endnote-26) Dong has developed an alternative Ir-catalyzed C-H activation-based branch selective process that offers promising levels of stereocontrol.[[27]](#endnote-27) Although elegant, these methods are not applicable to the issue at hand because they are reliant upon a condensation event to generate an enamine.

In this study, we outline an alternative approach that is predicated on using the glycine-based N-H unit as a directing group (**I**) to trigger metal-catalyzed “soft” enolization en route to *geometrically defined* homochiral enolates of type **II** (Scheme 1B, box).[[28]](#endnote-28),[[29]](#endnote-29),[[30]](#endnote-30) At the outset, this proposition was considered tentative because of the low acidity of **I**. Nevertheless, based on our earlier studies involving N-directed C-C bond activation,[[31]](#endnote-31) we were drawn to diphosphine modified cationic Ir(I)-systems as mild Lewis acids for the proposed enolization process (**I** to **II**). A synergistic benefit of these systems resides in Takeuchi and co-workers’ observation that they can also promote the non-enantioselective (and mechanistically unclear) branch selective addition of highly activated 1,3-dicarbonyls across alkenes.[[32]](#endnote-32),[[33]](#endnote-33),[[34]](#endnote-34) Accordingly, our reaction design required the metal catalyst to activate both a relatively non-acidic pronucleophile and a non-polarized proelectrophile. As outlined below, the realization of this approach (a) addresses the immediate issue of accessing β-substituted α-amino acids, (b) offers a unique directing-group-based approach to the *direct* stereocontrolled α-alkylation of low acidity carbonyl compounds (Scheme 1C, Eqn 4), and (c) provides a broader cross-coupling framework for the by-product free and stereocontrolled installation of contiguous stereocenters, which is a formidable issue.16 During the evaluation of this manuscript, we reported enantioselective decarboxylative Takeuchi-type processes that use highly acidic and directing 2-aza-aryl acetates as the pronucleophile.[[35]](#endnote-35) Compared to this, the work described herein represents a major advance because it allows the α-alkylation of much less acidic C-H bonds, and the installation of contiguous stereocenters. Additionally, the directing mode has potentially wider generality and the processes are mechanistically distinct.

**Scheme 1. Introduction**



**Results and discussion:** As part of our early studies towards the envisaged process, we explored the potential C-H addition of amide based systems **1a-f** across styrene **2a** (600 mol%). Because the nature of the N-substituent was deemed to be a critical factor, a range of options were evaluated using Ir(cod)2BARF (5 mol%) and (*R*)-BINAP (**L1**) (5 mol%) in toluene at 130 °C (Table 1). Carbamate (**1a**), sulfonamide (**1b**), amide (**1c**), N-benzhydryl (**1d**) and free amine (**1e**) systems were all ineffective. In contrast, aniline-derivative **1f** did lead to α-alkylation product **3fa** in 86% yield, >30:1 branched:linear selectivity, 9:1 d.r. and 96:4 e.r. (Entry 1). To improve on this remarkable preliminary result, other chiral diphosphine ligands were assayed and this revealed that replacing **L1** with (*R*)-SEGPHOS (**L5**) was beneficial (Entries 2-9). Further studies established that 1,4-dioxane is an effective solvent, offering marginal improvements to enantioselectivity (Entries 10-14). The precise nature of the precatalyst is important: counterions that are more strongly coordinating than BARF are less effective (Entries 15-18), whereas use of an analogous Rh-complex was not successful (Entry 19). Using the combination of Ir(cod)2BARF and **L5**, we optimized the loading of styrene, leading to the conditions outlined in Entry 21, which use just two equivalents. The reaction temperature can be lowered to 110 °C (Entry 23), although subsequent scope studies were conducted at 130 °C. *In all entries, branched to linear selectivities exceeded 30:1.*

We have explored the scope of the process, and found that it is effective for the coupling of a range of secondary and tertiary amide-based systems (**1f-l**) with styrene **2a** (Scheme 2A). Primary amides also participate with high enantioselectivity, but in more modest yield (Scheme S1). Notably, ketone-based systems also participate; for example, using (*R*)-3,5-(*t*-Bu)2-8H-BINAP as the ligand (not depicted), phenyl ketone-based adduct **3ma** was accessed in good yield, high diastereoselectivity and with promising enantioselectvity. Using **L7** as the ligand, methyl-ketone-based system **3na** was generated in 90:10 e.r.; here, C-C bond formation occurred at the *more hindered* side of the ketone, demonstrating a further benefit of the directing group controlled approach. The method even tolerates very hindered ketones, such that *t*-butyl system **3oa** could be accessed in high yield. The scope of the directing N-aryl unit has been investigated, and this revealed that a broad range of systems are viable (Scheme 2B). Of particular note is the success of N-4-hydroxylphenyl (**3pa** and **3wa**) and N-4-methoxyphenyl systems (**3qa**), as the aryl units of these products can easily be removed (vide infra). The method also offers very wide scope with respect to the styrene coupling partner (Scheme 2C). A variety of electron rich and electron poor systems participated smoothly, including those possessing sterically demanding

**Table 1. Reaction discovery and development.**



*a* Measured by 1H NMR using 1,3,5-trimethoxybenzene as the internal standard. *b* Determined by chiral SFC analysis. *c* Determined by 1H NMR analysis of the reaction mixture. *d* 1,2-DCP = 1,2-dichloropropane. *e* 2.5 mol% of the precatalyst was used. *f* The reaction was performed at 110 °C.

**Scheme 2. Scope of the hydroalkylation process.**



*a* (*R*)-3,5-(*t*-Bu)2-8H-BINAP was used as ligand. *b* The reaction temperature was 90 °C. *c* (*R*)-DTBM-SEGPHOS (**L7**) was used as ligand. *d* The reaction temperature was 140 °C and amide starting material was recovered in 35% yield. *e* Alkene (1000 mol%), (*R*)-DM-SEGPHOS (**L6**) (10 mol%) and [Ir(cod)2]BARF (10 mol%) were used at 110 °C in mesitylene.

*ortho*-substitution (e.g. **3fl**). Heteroaryl and ferrocenyl substituted systems **2f** and **2g** cross-coupled with high degrees of efficiency. Notably, α-olefins can also participate smoothly, although these less reactive proelectrophiles require more readily enolizable ketone-based systems. **L6** offered optimal efficiencies for *t*-butyl ketone **1o**, delivering targets **3op-3ot** in 71:29 to 96:4 e.r. and 2:1 to16:1 d.r. The tolerance of the protocol to a wide range of alkene coupling partners bodes well for further development and applications. To highlight the potential of the method for complex molecule synthesis, we prepared indomethacin derived styrene **2t**. Exposure of this to **1f** under optimized conditions delivered target **3ft** in 63% yield, 98:2 e.r., >30:1 branched to linear selectivity and 10:1 d.r. (Scheme 2D). Although the protocol tolerates very sensitive functionality (e.g. the -BPin unit of **3fh**), certain limitations (e.g. alkenes attached to basic heteroarenes, 1,1- and 1,2-disubstituted alkenes, *ortho-*substituted -NHAr units) have been identified and these are summarized in Scheme S2.

The initial alkylation products are readily derivatized to a range of potentially valuable amino-containing building blocks. For example, reductive manipulations of morpholino-amide **3ka** provided selective access to the corresponding amino alcohol **4**, aldehyde **5** and amine **6** (Scheme 3). Weinreb-amide-like ketone syntheses are also possible, as demonstrated by the formation of **7**.[[36]](#endnote-36)Hydrolytic decarboxylation provided chiral amine **8** in 97:3 e.r.; decarboxylations of this type are unusual, and further studies are being undertaken to rationalize the facility of this process.[[37]](#endnote-37) Systems possessing 4-hydroxyphenyl units on nitrogen can easily be deprotected to the free amine under oxidative conditions. For example, treatment of **3pa** with PIFA provided amino-amide **9** in 96% yield (Scheme 3B). Derivatization of this to its corresponding *p*-bromophenyl amide **10** allowed the determination of relative and absolute configuration by single crystal X-ray diffraction; the stereochemistry of other catalysis products was assigned on this basis. Hydrolysis of the amide of **9** provided the corresponding amino acid **11**, which is a critical subunit in a range of biologically relevant targets, including peptide β-turn mimics,[[38]](#endnote-38) endomorphin analogues,[[39]](#endnote-39) and the natural product bottromycin A2 (depicted).[[40]](#endnote-40) Compared to previous syntheses, this method for accessing **11** is notable for both its brevity and the level of stereocontrol. N-Deprotection of **3la** provided **12**, which maps onto the subunit of MEK kinase inhibitor candidates.[[41]](#endnote-41) Similarly, we were able to access the subunit of a growth hormone promoter candidate by devising a two step conversion of **1p** to **13**.[[42]](#endnote-42) The ability to access chiral amines by decarboxylation of the initial catalysis products was exploited in the conversion of **1w** to **14** via **3wk**, offering access to the key subunit of the weight loss drug (*S*)-lorcaserin.[[43]](#endnote-43)

Control experiments have confirmed that C-C bond formation requires the Ir-complex, the carbonyl unit and an NHAr unit (Scheme S3). Exposure of **1f** and **2a** to optimized conditions but in the presence of D2O resulted in deuterium incorporation at C2 of both the product ***deuterio*-3fa** and the starting material ***deuterio*-1f** at partial conversion (Scheme 4A, Eqn 1). Significant incorporation was also observed in the N-methyl groups, likely via reversible amide directed C-H activation of this position (Scheme S4).[[44]](#endnote-44) In the absence of the Ir-complex, no deuterium incorporation was observed at C2 (Eqn 2). Resubjection of diastereomerically pure product **3fa** to the reaction conditions in the presence of D2O resulted in no epimerization and no deuterium incorporation at C2 (Eqn 3), although incorporation was observed at the methyl groups (***deuterio*-3fa’**), presumably as a result of reversible amide directed C-H activation. Collectively, these results indicate that the envisaged Ir-catalyzed enolization of **1f** is feasible, whereas the product is resistant to this process, presumably because of the significant A(1,3)-strain that would arise in the resulting enolate. Efforts to isolate and characterize a chelate related to **I** or **II** have so far been unsuccessful, with NMR experiments indicating that this is not a resting state for catalysis. Using alkene **2j** as the limiting reagent, natural abundance 13C KIEs were determined according to the Singleton method (Eqn 4).[[45]](#endnote-45),[[46]](#endnote-46) Significant KIEs were observed at C1 (1.013) and C2 (1.008). Based on this, we currently favor a mechanism involving turnover limiting carbometallation from an Ir-π-complex. Accordingly, our working mechanistic framework is outlined in Scheme 4B. To initiate the process, N-H metallation of **1** provides **I**; related metallations have been demonstrated within the context of C-C bond activation processes using cationic Rh(I)-complexes.31 In the current scenario, the N-metallated unit of **I** functions as a Lewis acid to trigger enolization and provide **II**. At this stage, the Ir-center may or may not be deprotonated, with the former option depicted in Scheme 4B. Deprotonation could be facilitated by the -NHAr unit of another molecule of **1**; note that exogenous bases (e.g. Et3N, K2CO3) are detrimental to reaction efficiency. Our observations suggest the carbonyl unit must either be strongly coordinating (e.g. an amide) to enhance access to **I**, or relatively acidifying (e.g. a ketone) to facilitate enolization (cf. **I** to **II**). Thus, amide or ketone-based systems are effective, whereas, at the current level of development, ester analogues are not suitable. To facilitate carbometallation, the alkene component is then activated by π-coordination to either **II** or another Ir-center (**III**). To distinguish these options, graphical kinetic analysis was undertaken revealing the order in catalyst to be approximately 2 (Figure S1).[[47]](#endnote-47) Accordingly, we favor a bimetallic pathway leading to **IV**, which then undergoes protodemetallation to release the product. Although not depicted, one or other of the Ir-centers of **IV** may be coordinated to the carbonyl unit. The primary factor that governs enantioselectivity is likely the chiral information embodied within the Ir-enolate **II** because this is proximal to both reaction partners in the C-C bond forming step. The structural features of the substrate **1** and -coordinated alkene complex **III** are both likely to have a significant influence on the diastereoselectivity of the process. The high branch selectivity during the conversion of **II** to **IV** may reflect electronic effects and/or a preference for the Ir-center of **III** to move to the less hindered end of the alkene.

**Outlook and conclusions:** The mechanistic analysis outlined in Scheme 4B raises many interesting possibilities for future development. For example, an intriguing option is to investigate whether the pronucleophile and the proelectrophile can be activated using two different metal complexes. This would raise interesting possibilities for effecting stereocontrol. Perhaps more simply, the current catalyst system might be suitable for a wider range of directing modes. To probe this, we investigated the α-alkylation of amide **15**, where the directing group is moved one methylene unit further from the carbonyl unit (Scheme 4C). Remarkably, using styrene as the coupling partner, we were able to generate target **16** in 55% yield and with promising levels of selectivity.[[48]](#endnote-48) Clearly further refinement is required, but the result is important because it shows that the directed enolization approach has wider applicability. More broadly, our study is significant because enantioselective C(sp3)-H additions to alkenes are achieved by exploiting “native” directing functionality. This has a clear parallel to Murai’s seminal *ortho*-directed alkene hydroarylations,[[49]](#endnote-49) a report that ignited the field of metal-catalyzed C(sp2)-H functionalization, and has led to an emerging family of by-product free enantioselective cross-couplings.[[50]](#endnote-50) Our laboratory is now focussed on developing a complementary set of C(sp3)-H-based cross-couplings by harnessing the design principles outlined here.

**Scheme 3. Derivatizations and additional scope.**



*a* LiAlH4 (200 mol%), THF, 0 °C, 20 min then NaBH4 (400 mol%), MeOH, 0 °C to r.t., 1 h. *b* LiAlH4 (200 mol%), THF, 0 °C, 20 min. *c* BH3•THF (500 mol%), THF, 90 °C, 4 h. *d* PhLi (200 mol%), THF, 0 °C, 15 min. *e* H2SO4/AcOH/H2O, 120 °C, 72 h. *f* [Bis(trifluoroacetoxy)iodo]benzene (120 mol%), MeCH/H2O, 0 °C, 1 h. *g* HCl/AcOH, 130 °C, 48 h. *h* 4-Bromobenzoyl chloride (100 mol%), Et3N (200 mol%), DCM, 0 °C to r.t., 12 h. *i* NaH (200 mol%), DMA, 60 °C, 3 h. *j* HCl/AcOH, 150 °C, 72 h.

**Scheme 4. Mechanistic analysis leads to further scope.*a***



*a* Further control experiments and mechanistic discussion are given in the Supplementary Information.

**Supplementary Information and Data Availability**

The Supplementary Information document contains: Schemes S1-4 and Figure S1, analytical data listings and NMR spectra. CCDC 2245009 and 2246104 contain crystallographic information for this manuscript.

**Competing Interests**

The authors declare the following competing interests: A patent has been filed by the University of Liverpool on the chemistry described in this manuscript (“Alkylation Process,” UK Patent Application No. 2306313.4).

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**Author Contributions**

F.H. evaluated reaction conditions and conducted mechanistic studies. F.H. and T.P.A. evaluated reaction scope. All authors analyzed data. P.D.K. and J.F.B. designed and directed the work. J.F.B. wrote the manuscript with contributions from all the authors.

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