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Review

An overview on the organocatalytic aza-benzoin condensation reactions

Domenico C. M. Albanese[1], and Nicoletta Gaggero [2,*]

[1] Department of Chemistry, Università degli Studi di Milano, via Golgi 19, 20133-Milano, Italia; domenico.albanese@unimi.it

[2] Department of Pharmaceutical Sciences, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, via Venezian 21, 20133-Milano, Italia. E-mail: nicoletta.gaggero@unimi.it.

* Correspondence: e-mail@e-mail.com; Tel.: +39-0250314470

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Abstract: The N-heterocyclic carbenes (NHCs) catalyzed aza-benzoin condensation reaction is an efficient, single step strategy which employs easily available substrates such as aldehydes and imines to provide α-amino ketones. The multi-functionality and high reactivity of α-amino ketones make these structures attractive for medicinal chemistry and as precursors of a variety of amine derivatives. The different electrophilic character of aldehydes and imines ensures a high regioselective reaction. Enantiomerically enriched α-amino ketones have been synthesized through stereoselective couplings promoted by chiral N-heterocyclic carbenes. One-pot domino procedures including an aza-benzoin step allow access to valuable complex molecules.

Keywords: aza-benzoin condensation; N-heterocyclic carbene; alpha-aminoketone; organocatalysis, imine, bis(amino)-cyclopropenylidene

1. Introduction

α-Amino ketones are widespread structural moieties common to both natural and synthetic significant compounds in medicinal chemistry (Figure 1) [1–4].

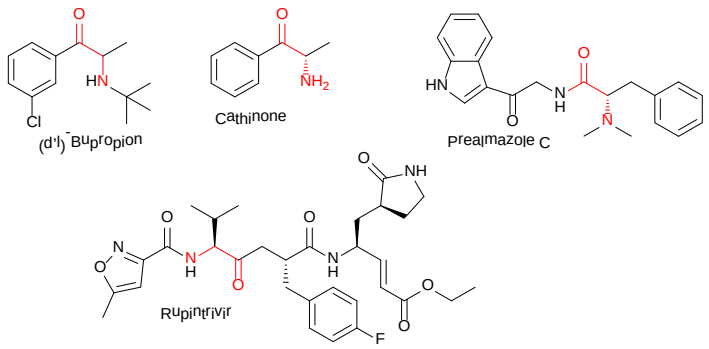
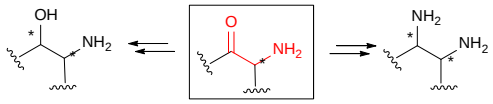


Figure 1. Synthetic and natural biologically active α-amino ketones.

They are largely employed as building blocks for the preparation of a large number of molecules and in particular 1,2-aminoalcohols, and vicinal diamines (Scheme 1), important motifs in many pharmaceutical compounds and widely applied as chiral auxiliaries and ligands in the field of asymmetric synthesis [5,6]. Moreover, they are precursors in the preparation of many heterocycles [7-11] and smoothly undergo nucleophilic addition reactions to give a variety of derivatives [12].

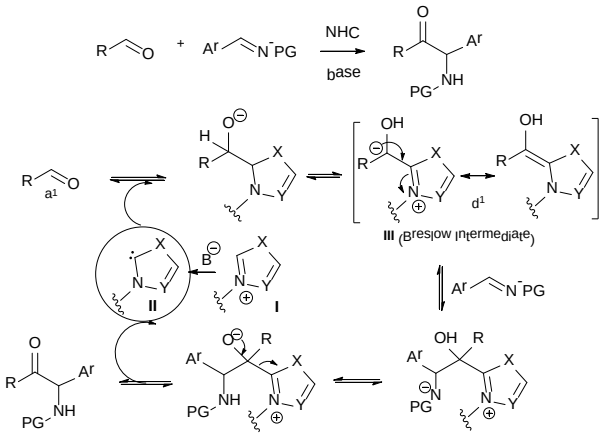


Scheme 1. Synthetic potential of α-amino ketones.

Numerous synthetic routes to α-amino ketones are reported in the literature. However, these methods involve longer multistep transformations starting from functionalized reactants such as α-azido ketones [13], α-nitro ketones [14] or α-amino acids [12, 15].

The aza-benzoin condensation reaction, strictly related to the well-known benzoin condensation reaction, represents the more straightforward approach to α-amino ketones and occurs with 100% atom economy.

In its most general form, the aza-benzoin condensation reaction, firstly reported in 1988 [16] is a N-heterocyclic carbene (NHC) catalyzed coupling between an aldehyde and an activated imine (Scheme 2). The mechanism of this process, in analogy with the benzoin condensation, envisages the formation of a nucleophilic NHC **II** from azolium salt **I**, under basic conditions. Its addition to aldehyde followed by proton transfer generates an acyl anion equivalent **III** known as Breslow-Intermediate, thus causing a reversal of the original electrophilic carbonyl reactivity, universally known as umpolung (dipole inversion). The acyl anion equivalent can be stabilized by the π-back-donation of the carbanion onto the empty p_z orbital of the carbene atom giving rise to hydroxy-enamine-type Breslow Intermediate (Scheme 2).



X = S, NR^2; Y = CR^3, N; R = Alkyl, Aryl; PG = protecting group
a^1 = electron acceptor synthon (positively polarized carbon atom); d^1 = electron donor synthon (negatively polarized carbon atom)
The superscript indicates that the carbon atom C-1 of the functional group itself is the reacting one as a d^{1-} or a^{1-}synthon.

Scheme 2. Catalytic cycle of the aza-benzoin condensation

The nucleophilic attack of Breslow Intermediate to the electrophilic imine, a second proton transfer step and subsequent elimination furnish the condensation product at the same time regenerating the catalyst. The wide choice of chiral azolium salts reported in the literature allows access to the asymmetric version of the reaction affording enantioenriched α-amino ketones [17]. Besides NHCs also bis(amino)-cyclopropenylidenes (BACs) have been successfully applied as umpolung promoting species [18].

Recently, increased attention has been turned to the nature of the nucleophilic partner including acylsilanes as acyl donors.

The scope of this review article is to provide an overview of the advances in chemoselective aza-benzoin condensation reactions, covering methods to both racemic and enantiomerically enriched α-amino ketones. The synthesis of more complex molecules *via* tandem reactions which involve an aza-benzoin coupling step is also described.

At last, the synthesis of a selected pharmaceutical candidate which employ the aza-benzoin condensation as the key reaction of the process is considered.

2. Chemoselective aza-benzoin condensation reactions

The major issue to successfully execute the aza-benzoin condensation reaction is the requirement that the whole process should evolve under kinetical control, where the imine is more reactive towards Breslow Intermediate than a second molecule of aldehyde, but less reactive if compared to aldehyde with the NHC catalyst.

Activated imines (Figure 2) are often employed in organic chemistry as equivalents of carbonyl compounds in reactions with a wide array of nucleophilic reagents [19-21].

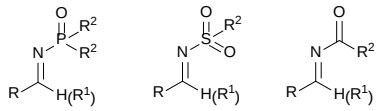
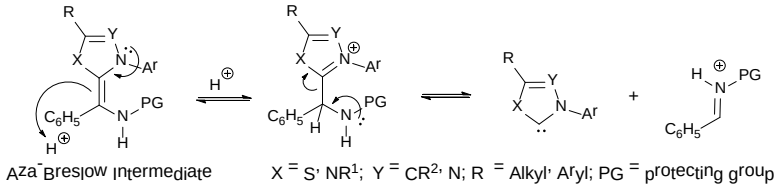


Figure 2. Some activated imines.

Compared to the controlled cross-acyloin reaction between two different aldehydes [22], the use of imines as acyl anion acceptors is advantageous due to the difference in electrophilicity between aldehydes and imines and to the possibility of further finely adjusting imine reactivity because of the trivalency of nitrogen. The choice of the imine protecting group is critical. In fact, the carbene addition to activated N-tosyl and N-phosphinoyl imines to give a stable nitrogen analogues of Breslow Intermediate that could stop the catalytic cycle, has been found [23]. However, recent studies have shown that a fast dissociation-recombination process of the carbene/iminium ion pair takes place in the presence of an acid catalyst (Scheme 3) [24-25].

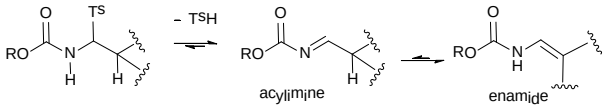


Scheme 3. Fast dissociation-recombination of aza-Breslow intermediate.

Arylsulfonylamides and tert-butyl- or benzyl aryl(tosyl) carbamates have been widely employed as imine precursors thank to their simple preparation, high stability and to the aptitude to provide in situ the reactive imines under mild conditions. Moreover, the introduction of alkoxycarbonyl functionalities (e.g. Boc or Cbz) as activating groups allows to obtain the final amino derivatives which can be easily deprotected.

The substrate scope is presently limited to aldimines deriving from aryl or heteroaryl aldehydes. Conversely, imines obtained from aliphatic aldehydes undergo decomposition or tautomerization to the more stable enamine derivatives and their use has not yet been realized (Scheme 4).

Commento [D1]: enamide



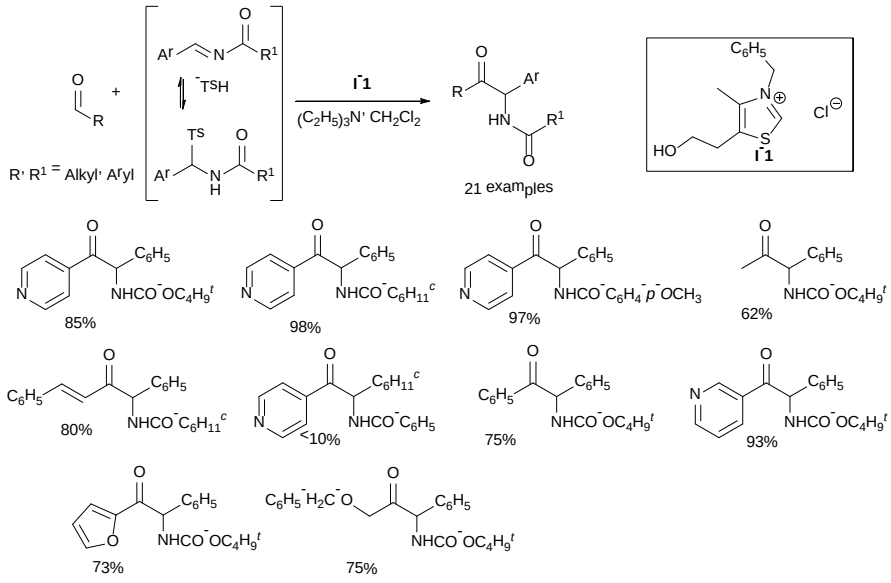
Scheme 4. Imine/enamide equilibrium.

On the other hand, ketimines are of particular interest because they serve as precursors of tetrasubstituted carbon atoms. However, their utilization have proved to be more challenging due to their poor reactivity.

3. Methods to racemic α-amino ketones

3.1 Use of N-heterocyclic carbenes

Murry and co-workers envisioned to carry out the coupling of N-benzylidene cyclohexanecarboxamide, slowly generated *in situ* from the parent α-amido sulfone by elimination of sulfinic acid in order to ensure catalyst turnover, with 4-pyridinecarboxaldehyde in the presence of commercially available thiazolium salt **I-1** and triethylamine (Scheme 5). Under these conditions the corresponding amino ketone was obtained with 98% yield [26].



1-1 equiv of aldehyde, 10 mol% of precatalyst, 15 equiv of $(C_2H_5)_3N$, CH_2Cl_2, 35 °C, 15 min-24 h

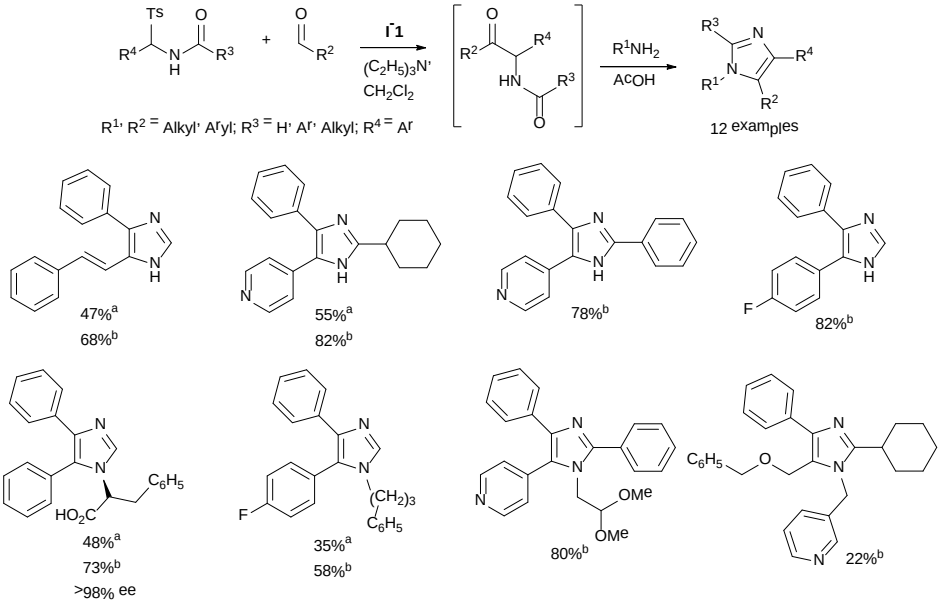
Scheme 5. Murry and co-workers selected examples of aza-benzoin condensation between acylimines and aldehydes.

The reaction displays a wide scope with respect to the aldehyde. It is noteworthy that α,β-unsaturated cinnamaldehyde, under these reaction conditions, did not undergo 1,4-addition and also aliphatic acetaldehyde reacts although in moderate yield (Scheme 5).

The process is tolerant also to the amide portion of the tosylamide. However, tosylamides deriving from aliphatic aldehydes bearing an α-proton failed to generate the corresponding acylimines likely due to the aptitude of these compounds to isomerize to enamides.

Cross-over experiments highlighted that the reaction is under kinetic control and that the corresponding benzoins are not observed and do not serve as substrates.

Subsequently, Murry disclosed the application of his methodology to a novel one-pot synthesis of highly functionalized imidazoles, an important class of heterocycles widespread in natural products and in medicinal chemistry (Scheme 6).



[a] Product isolated by crystallization from the crude product mixture. [b] Product isolated by chromatography.

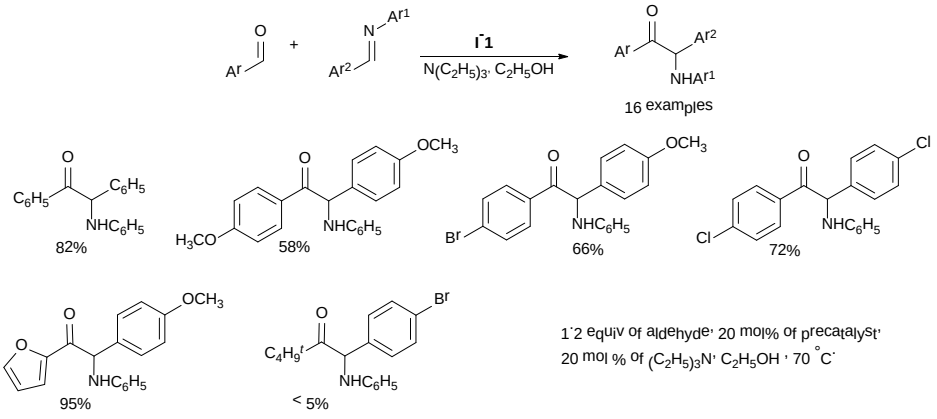
Scheme 6. Murry and co-workers selected examples of one-pot synthesis of imidazoles.

The addition of an appropriate amine and acetic acid to the reaction mixture of the α-amino ketone intermediate followed by heating to reflux provided the ring closure to imidazole. Moreover, chiral imidazoles can be prepared starting from chiral amines or amino acids. It is noteworthy that tetra substituted imidazoles, difficult to obtain by other routes, can be synthesized with moderate to good yields by this methodology. This approach allows access also to substituted oxazoles and thiazoles in good yields by replacing the amine with triphenylphosphine/iodine or the Lawesson's reagent, respectively [27].

Pseudo-homo-couplings (defined as an aldehyde reacting with an imine derived from the same aldehyde, Ar = Ar^2) and cross-couplings (Ar ≠ Ar^2) under thermodynamic control have been developed some years later by using unactivated aryl imines, aryl aldehydes, thiazolium salt **I-1** as the precatalyst and triethylamine as the base, in refluxing ethanol for 48 hours (Scheme 7).

Under these conditions competing benzoins could reversibily form and behave as substrates for α-aminoketones formation.

Cross experiments highlighted that also the α-aminoketone formation is reversible. This protocol provides the access to aza-benzoin coupling also by less reactive aryl imines [28].

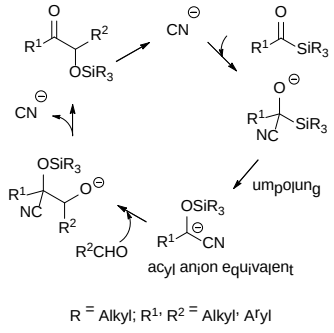


Scheme 7. You and coworkers selected examples of intermolecular coupling between unactivated imines with aldehydes.

Acylsilanes, disclosed by Brook in 1957, are considered as sterically hindered aldehydes by virtue of the removable silyl group and undergo smoothly nucleophilic addition reactions [29]. They have been employed as unconventional donor partners in regioselective intermolecular acyloin condensation in a number of procedures catalyzed by cyanides [22].

In the benzoin-type condensation reaction, after the nucleophilic attack of the cyanide catalyst on the acylsilane, the mechanism involves a [1,2] shift of the migrating SiR_3 group (Brook rearrangement) generating the key stabilized acyl anion equivalent, in analogy with Breslow catalytic cycle.

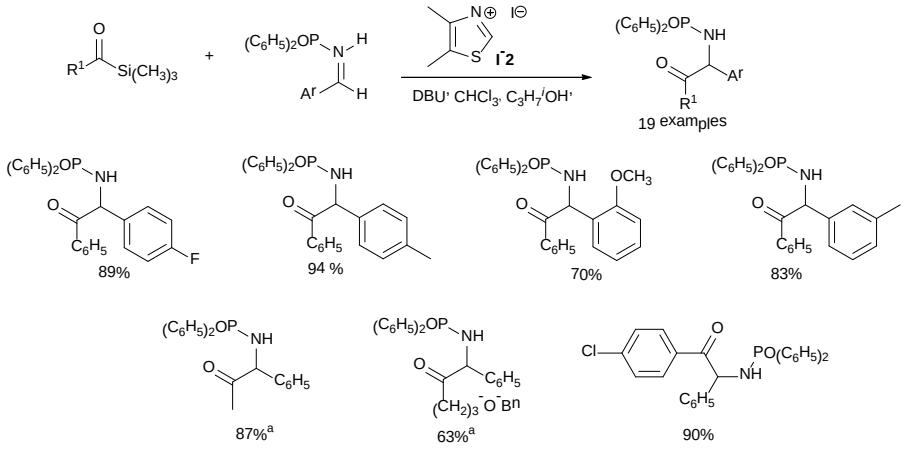
The subsequent addition of this species to the competent electrophile, followed by catalyst release, leads to the desired condensation product (Scheme 8).



Scheme 8. Acylsilanes as acyl donors in cross benzoin condensation.

Scheidt disclosed the reaction of alkyl and aryl acylsilanes with aromatic N-diphenylphosphinoyl imines upon exposure to catalytic N-methyl 4,5-dimethyl thiazolium salt (**I-2**) (30 mol%), DBU as the base and a stoichiometric amount of *iso*propanol for 48 hours. Under these new conditions, the Brook rearrangement occurs smoothly without the need of charged and potentially toxic cyanide, fluoride or phosphite anions [30].

177 N-phosphinylated amino ketones, completely devoided of any homo-coupling product
178 contamination in 51-94% yields have been afforded (Scheme 9).



2 equiv of acylsilane, 30 mol % of precatalyst, 30 mol % of DBU, 4 equiv of alcohol, $CHCl_3$ 60 °C.
[a] dimethylphenyl acylsilane was used.

179

180 Scheme 9. Scheidt and co-workers selected examples of aza-benzoin coupling between acylsilanes
181 and N-diphenylphosphinoyl imines.

182 The phosphinoyl group on the nitrogen atom can be removed at the end of the reaction under
183 mild conditions to give α-aminoketones. Alkyl N-phosphinoyl imines have been unsuitable for the
184 reaction since they undergo isomerization to more stable enamides due to the presence of an
185 enolizable proton. On the other hand, N-phosphinoyl protecting group is essential for the success of
186 the reaction. In fact, more reactive N-benzoyl, N-sulfinyl and N-sulfonyl imines interact irreversibly
187 with the catalyst thus stopping the catalytic cycle. NHCs derived from imidazolium or triazolium
188 salts did not afford the desired reaction. The proposed mechanism, illustrated in Scheme 10,
189 envisages the addition of carbene **II-2** to acylsilane followed by the formation of intermediate **IV** *via*
190 Brook rearrangement. The reaction of this intermediate with the imine is reversible and thus
191 unproductive. The subsequent transfer of $Si(CH_3)_3$ to *iso*propanol provides less congested
192 intermediate **III-2** (Breslow Intermediate) that, after imine addition, affords the protected α-amino
193 ketone and regenerates the catalyst.
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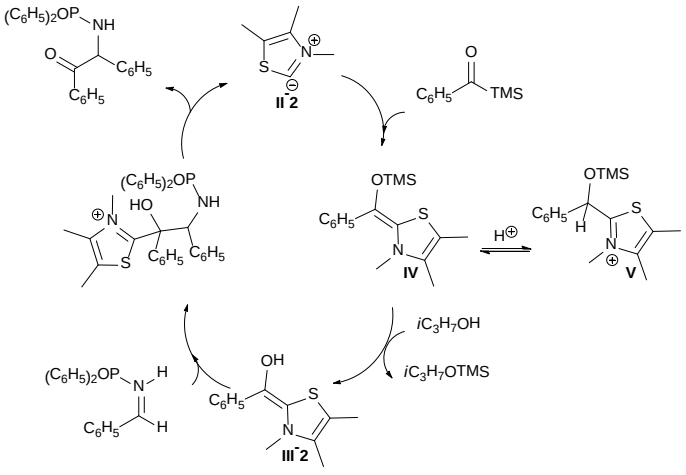

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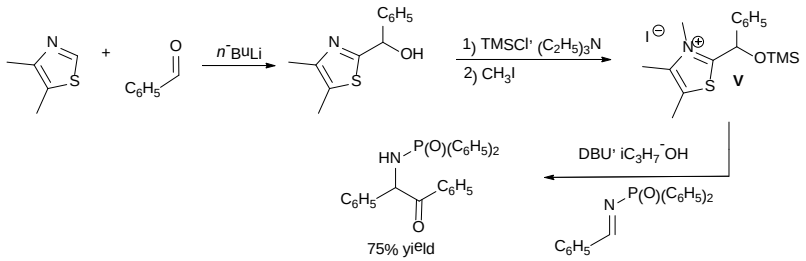
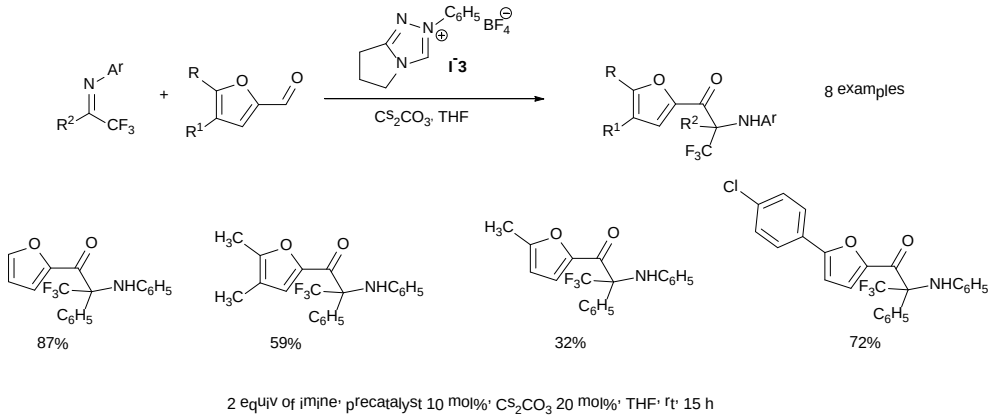
Scheme 10. Catalytic cycle of acyloin-type coupling between acylsilanes and N-aryldiphenylphosphinoyl imines.

An independent synthesis of intermediate **V** and its reaction with N-(diphenylphosphinyl) benzaldimine in the presence of DBU and *iso*propanol to give the desired product provided substantial evidence for the proposed catalytic cycle (Scheme 11) [30]. This strategy opened a new access, induced by neutral carbenes, to the Brook rearrangement.



Scheme 11. Synthesis and reactivity of intermediate **V**.

Non-enolizable N-protected aryl trifluoromethyl ketimines have been used as acceptor partners in the coupling with a series of highly reactive furan-2-carbaldehydes to give the corresponding α-amino-α-trifluoromethyl ketones, bearing a valuable quaternary stereocenter, in moderate to good yields (32-87%) in the presence of triazolium salt **I-3** (Scheme 12) [31].



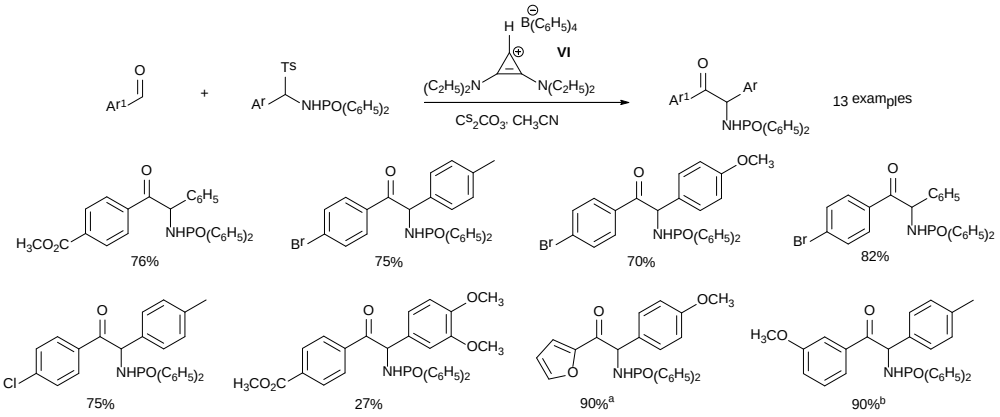
Scheme 12. Enders and co-workers selected examples of trifluoromethyl ketimines and aldehydes couplings.

3.2 Use of bis(amino)-cyclopropenylidenes (BACs)

N-heterocyclic carbenes have emerged as powerful, efficient and versatile organocatalysts, which still are allowing access to new and unexpected organic trasformations. The efforts in developing non five-membered nitrogen containing heterocyclic carbenes have been rather limited as a consequence of NHCs success. However, bis(amino)-cyclopropenylidenes (BACs), the smallest aromatic rings containing a carbene center, have recently been employed in some intriguing applications [32,33]. Easily prepared in a one-pot reaction, BACs, likewise NHCs, catalytically induce acyl anion reactivity in aldehydes. Moreover, a significant amount of aldehyde

self-condensation side product is often formed in NHCs chemistry whereas it is normally absent in umpolung reactions catalyzed by BACs.

The limited ability of BACs to mediate aldehyde couplings even under ideal conditions prompted the exploration of their potential in aza-benzoin reactions. After fruitless attempts with Boc and tosyl imines, P,P-diphenyl N-[(aryl)(tosyl)methyl] phosphinic amides, the more practical surrogates of the corresponding protected imines, gave productive results in the reaction with aromatic aldehydes in the presence of bis(diethylamino)cyclopropenium salt **VI** (Scheme 13) [18].



Scheme 13. Gravel and co-workers selected examples of enantioselective aza-benzoin condensation catalyzed by BACs.

The reaction is effective with heteroaromatic, *para* or *meta* substituted benzaldehydes. In some cases an excess of aldehyde has been necessary to drive the reaction towards the product.

Both electron-poor and electron-rich groups on the *para* position of the aromatic ring of the acceptor are compatible with the reaction. Although the acidic deprotection of phosphinic amides can be performed under mild conditions, the product proved not to be stable as the free base, therefore it was necessary to insert again the nitrogen protecting group.

Until now, attempts to develop the asymmetric version of the reaction using a chiral BAC have not reach the goal.

4. Methods to enantiomerically enriched α-amino ketones

The first example of asymmetric aza-benzoin reaction is due to Miller and co-workers which used an unconventional chiral thiazolium salt. Ideally it derives from histidine by replacing the imidazole ring with the thiazole one (Figure 3).

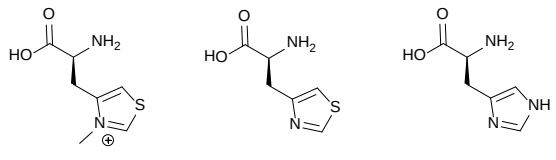
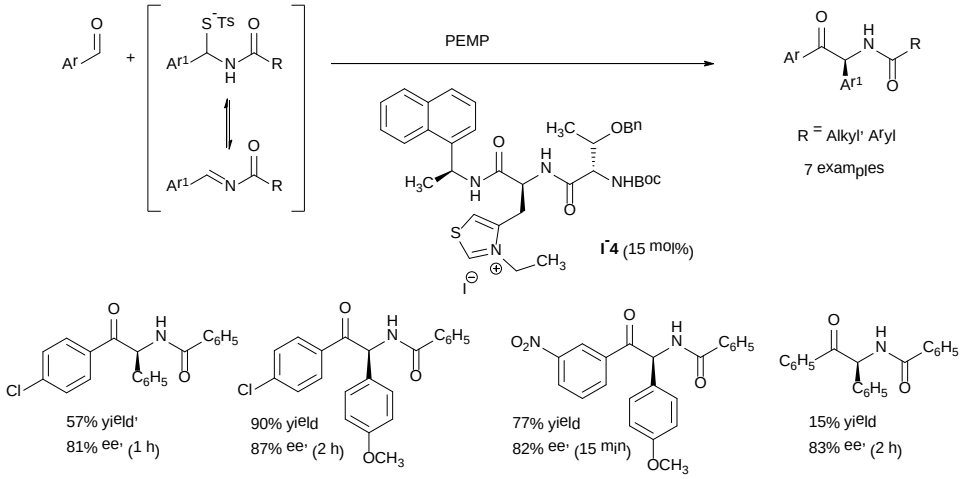


Figure 3. Thiazolium derivative and its precursors.

In order to ensure a chiral binding pocket to the reaction partners the thiazolylalanine has been inserted as the middle aminoacid in a tripeptide sequence and subsequently converted to the corresponding thiazolium salt.

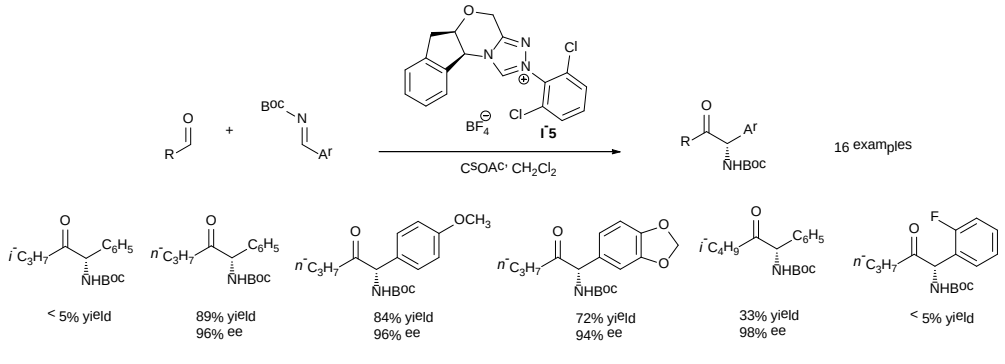
Enantiomerically enriched α-amino ketones have been obtained by the coupling of aromatic aldehydes with *in situ* generated acylimines in the presence of the chiral thiazolylalanine (Taz) containing peptide salt **I-4** (Scheme 14) [34].



Scheme 14. Miller and co-workers selected examples of enantioselective intermolecular aza-benzoin condensation catalyzed by salt **I-4**.

The reaction product undergoes to racemization under basic reaction conditions due to enolization. In order to ensure high enantiomeric excesses, the amount of amine and the reaction time need to be carefully evaluated.

The assumption that a less activated imine would lead to increased stability of the newly formed stereocenter prompted Rovis to employ N-Boc-protected imines in the presence of chiral **I-5** and aliphatic aldehydes (Scheme 15) [22].

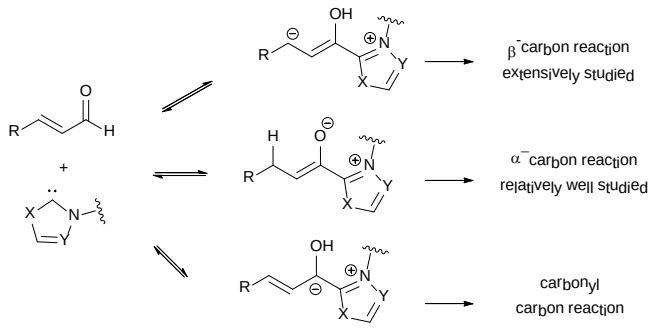


Scheme 15. Rovis and co-workers selected examples of enantioselective intermolecular aza-benzoin condensation.

Cesium acetate has been used as the base in order to generate *in situ* the catalytic amount of the acid required for catalyst regeneration. The reactions have been carried out at - 20°C to suppress racemization and molecular sieves have been added to prevent hydrolysis of imines due to the igroscopic nature of the salt. Following the optimization of the conditions, the scope of the reaction has been explored. Excellent ees and high yields have been obtained with a variety of straight chain aldehydes. On the other hand, lower yields have been observed when β-branched aliphatic aldehydes such as *iso*-butyraldehyde have been employed, whereas α-branched aldehydes do not react. Electron-rich and electron-poor Boc-arylimines have been used, however *ortho*-fluoro aryl derivative does not participate in the reaction.

One of the challenges of organic chemists is the ability to highlight different substrate reactivities in a selective manner.

The use of enals in cross-acyloin couplings is an arduous task since homoenolate, enolate and acyl anion equivalent can all be generated by reaction with NHCs through different reaction pathways (Scheme 16).

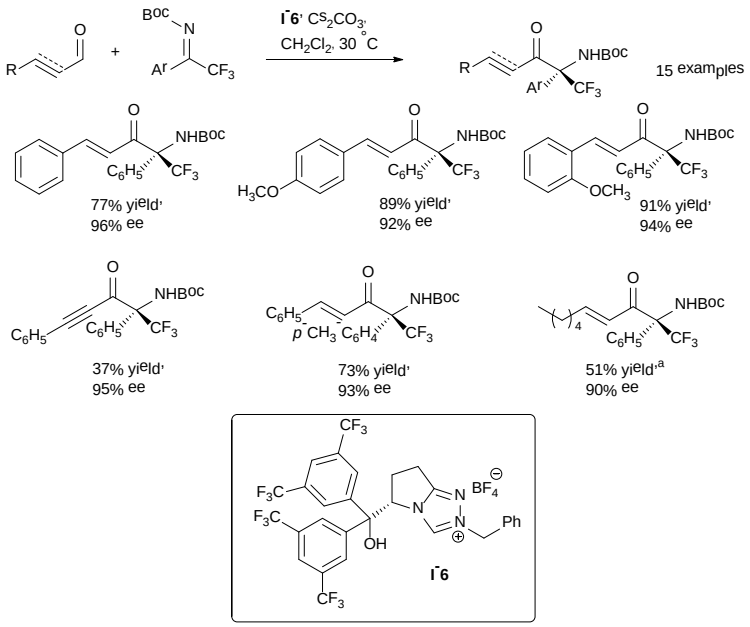


Scheme 16. Use of enals in NHCs chemistry.

The choice of the catalyst is the key factor that controls the chemoselectivity of these three species.

Ye studied the influence of steric and electronic factors of a series of L-pyroglutamic acid derived triazolium salts on the reactivity of cynnamaldehyde with N-Boc protected trifluoromethyl phenyl ketimine (Scheme 17) [35].

The free hydroxy group on the catalyst plays a key role not only for the reduced steric hindrance compared to its silylated analogous, but, more importantly, thanks to the possible hydrogen bond formation with the ketimine. The desired products have been obtained in high yields and enantioselectivities by using catalyst **I-10** (Scheme 17). Electron-withdrawing and electron-donating substituents on the aromatic ring of enals do not change yields and enantioselectivities. β-Alkyl enals worked well in the reaction, however β-alkyl and β-aryl ynals resulted in decreased yields, although high ees have still been obtained.

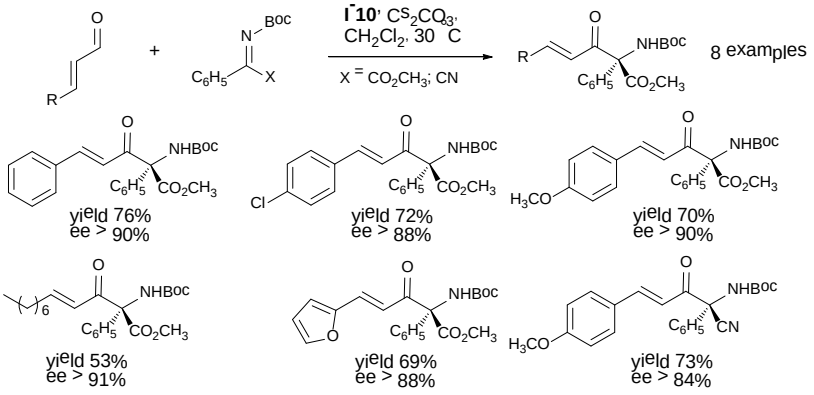


1.2 equiv of imine, 10 mol % of precatalyst, 20 mol % of Cs_2CO_3, CH_2Cl_2, 30 °C. [a] 10 mol% of Cs_2CO_3 was used.

Scheme 17. Ye and coworkers selected examples of enantioselective intermolecular aza-benzoin condensation using enals.

The free hydroxy group on the catalyst plays a key role not only for the reduced steric hindrance compared to its silylated analogous, but, more importantly, thanks to the possible hydrogen bond formation with the ketimine. The desired products have been obtained in high yields and enantioselectivities by using catalyst **I-10** (Scheme 17). Electron-withdrawing and electron-donating substituents on the aromatic ring of enals do not change yields and enantioselectivities. β-Alkyl enals worked well in the reaction, however β-alkyl and β-aryl ynals resulted in decreased yields, although high ees have still been obtained.

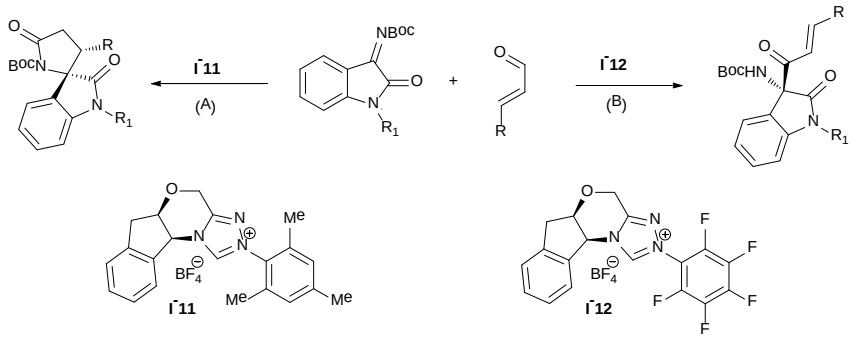
In order to further explore the scope of the reaction, (Z)-methyl 2-((*tert*-butoxycarbonyl) imino)-2-phenylacetate and (Z)-*tert*-butyl(cyano(phenyl))methylene) carbamate were used as acceptors. The aza-benzoin products have been obtained in good yields and high enantiomeric excesses (Scheme 18).



Scheme 18. Ye and coworkers selected examples of aza-benzoin reaction.

Cyclic N-protected ketimines have attracted significant interest, especially within asymmetric synthesis, due to their easy preparation and handling and their stable E/Z configuration which ensures a high enantiofacial differentiation. In particular, the oxindole scaffold is a privileged structural motif common in natural products and in pharmacological active compounds.

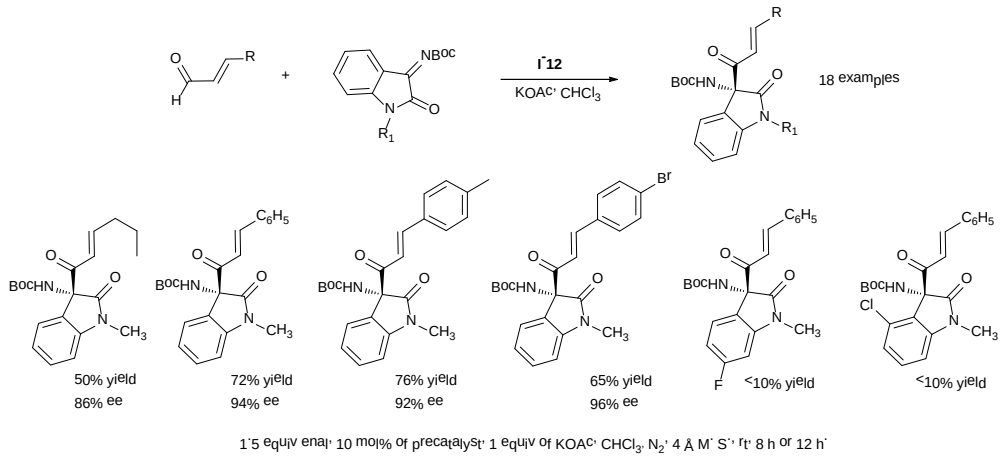
The chemoselectivity of the reaction between 2,3-dioxo-2,3-dihydroindole (isatin) derived ketimines and enals has been studied by Chi [36]. When precatalyst **I-11** was used, the reaction afforded the homoenolates derived adducts (pathway A). Replacing the encumbered and electron-rich N-mesityl substituent with less hindered and electron-deficient pentafluorophenyl moiety (**I-12**) switched the outcome of the reaction towards the aza-coupling product with high chemoselectivity (pathway B) (Scheme 19).



Scheme 19. Pathways deriving from reaction between enals and isatin-derived ketimines catalysed by NHCs. (A) β-carbon reaction. (B) Carbonyl carbon reaction.

Commento [D2]: ~~Possible~~ deleted

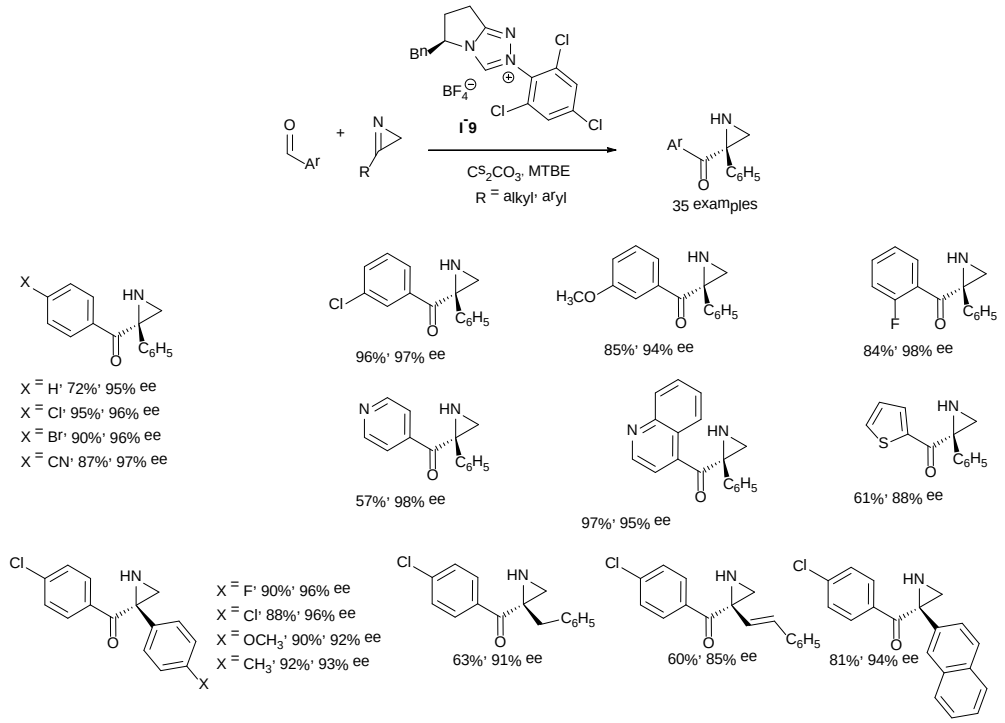
3-Aminooxindoles bearing a quaternary stereocenter with high ees and good yields have been prepared (Scheme 20).



1.5 equiv enal, 10 mol% of precatalyst, 1 equiv of KOAc, $CHCl_3$, N_2, 4 Å M.S., rt, 8 h or 12 h.

Scheme 20. Chi and co-workers selected examples of enantioselective intermolecular aza-benzoin reactions between enals and isatin-derived ketimines.

An unprecedented enantioselective aza-benzoin coupling starting from ring-strained 2*H*-azirines to give chiral aziridines, useful building synthons and valuable pharmaceutical structural motifs has been recently reported [37]. Functionalized benzaldehydes and heteroaromatic aldehydes are well tolerated (Scheme 21). Unfortunately aliphatic aldehydes failed to participate in the reaction (data not shown).



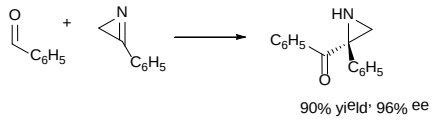
1.2 equiv of aldehyde, 15 mol% of precatalyst, 1 equiv of CS_2CO_3, MTBE, 25 °C, argon atmosphere.

Scheme 21. Reaction scope

The scope of the reaction has been also tested with respect to the 2H-azirines by systematically varying substituent patterns on the aromatic ring. In all cases high ee and yields have been obtained

When alkyl or alkenyl groups replaced the aromatic ring excellent enantiomeric excesses have been still achieved although with lower yields.

The scaling up of the reaction afforded excellent yields and ee (Scheme).

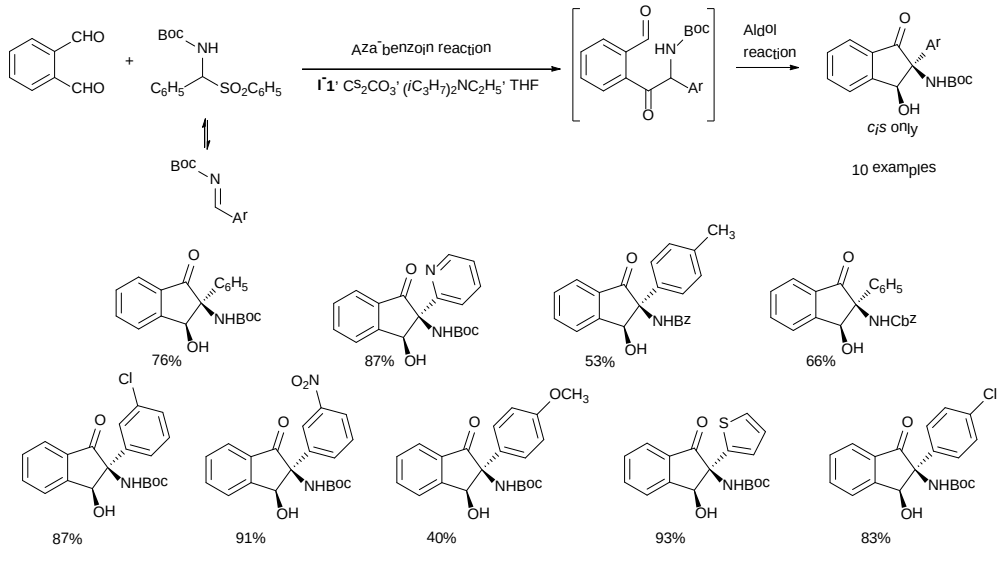


Scheme . Gram-scale synthesis.

5. Tandem reactions

In 2011, almost simultaneously, two papers dealing with the preparation of functionalized dihydroindenones with divergent diastereoselectivity have been published.

Ye and coworkers developed a tandem aza-benzoin/aldol reaction starting from benzene 1,2-dicarboxaldehyde and N-Boc imines using **I-1** as precatalyst which afforded exclusively *cis*-2-amino-3-hydroxyindenones with yields up to 93% (Scheme 22) [38].

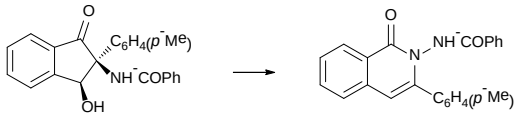


Scheme 22. Ye and co-workers selected examples of tandem aza-benzoin/aldol reactions.

Optimized conditions required the use of cesium carbonate to generate the carbene and di*iso*propylethylamine in order to promote the formation of the imine.

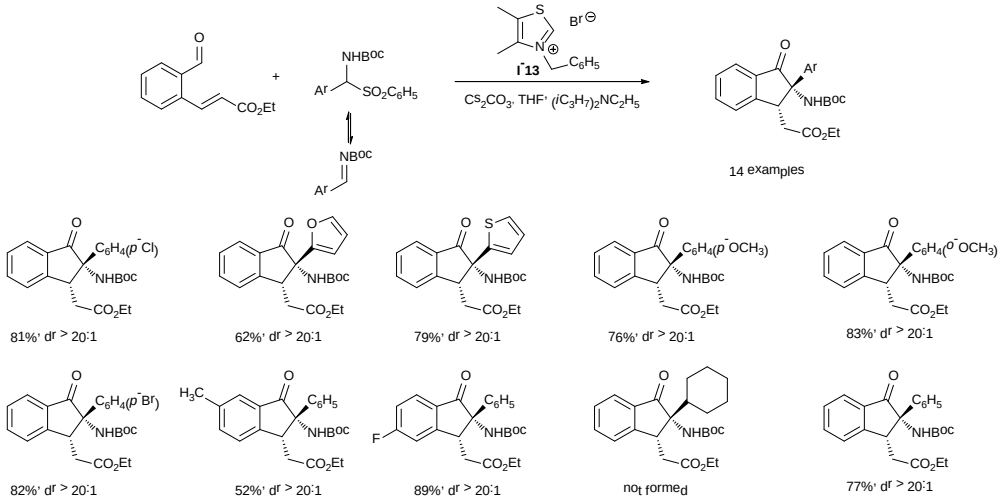
Phenyl imines with electron-withdrawing groups gave the corresponding indenones with higher yields compared to imines with electron-donating substituents. Imines bearing both a *m*-chlorophenyl or a *p*-chlorophenyl group showed similar reactivity. Also heteroarylimines gave high yields.

The resulting *cis* 1-hydroxy-3-oxo-2-(*p*-tolyl)-2,3-dihydro-1H-inden-2-yl)benzamide could be easily converted to the corresponding isoquinolinone under Mitsunobu conditions (Scheme 23) [38].



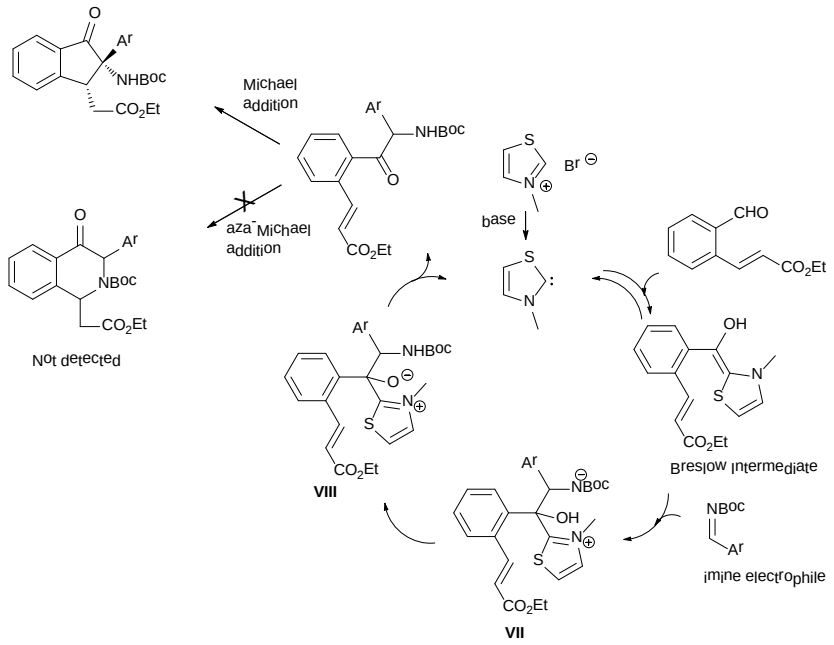
Scheme 23. Synthesis of isoquinolinone.

You and coworkers developed a process to substituted *trans* dihydroindenones through a NHC-catalyzed aza-benzoin/Michael reaction starting from *tert*-butyl aryl(tosyl) methylcarbamates and (*E*)-ethyl 3-(2-formylphenyl)acrylates (Scheme 24) [39].



Scheme 24. You and co-workers selected examples of tandem aza-benzoin/Michael reaction.

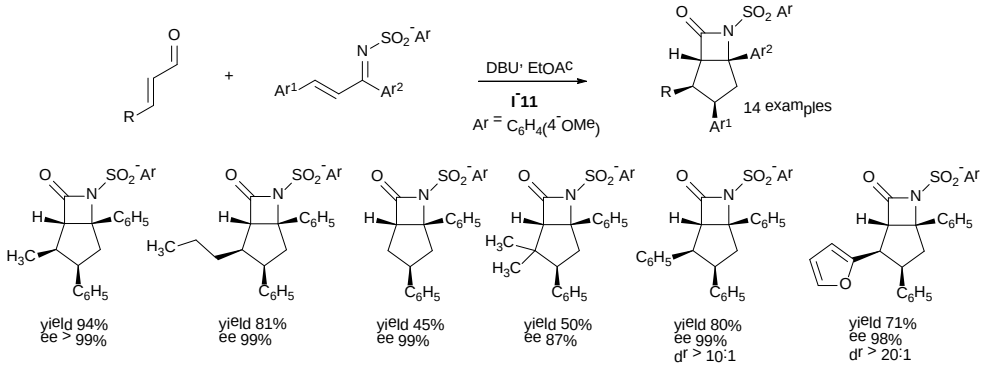
In order to obtain high yields of the desired product, 2.2 equivalents of cesium carbonate have been used. A reduced loading of base furnished some aza-benzoin product together with the dihydroindenone, while a further increasing the Cs_2CO_3 decreased the yield. Under the optimized conditions the tandem reaction tolerated both electron-withdrawing and electron-donating substituents on the phenyl group of the imine and also heteroarylimines gave good results. Cyclohexyl-substituted carbamate did not react. Also functionalized acrylates could be used as suitable substrates. ~~A possible~~ catalytic cycle is depicted in Scheme 25.



Scheme 25. Proposed catalytic cycle of tandem aza-benzoin/Michael reaction .

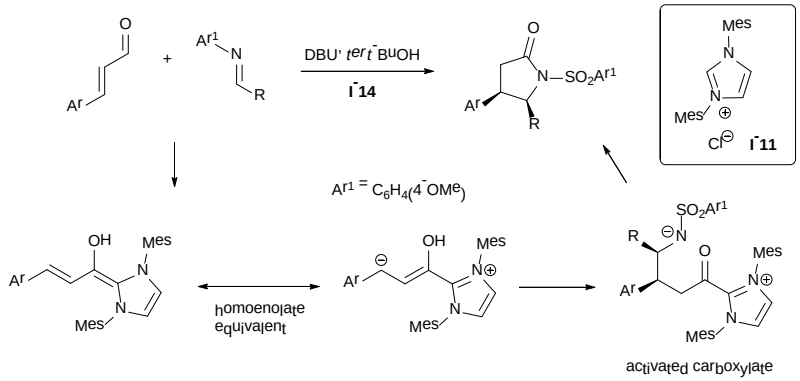
The Breslow Intermediate, generated from the reaction of the carbene catalyst with acrylate, produced the intermediate **VII** after addition of imine. A subsequent proton transfer gives intermediate **VIII**, which releases the catalyst and the α-amino ketone. It is worth noting that the imine carbon acts as an electrophile in the first step of the process when reacts with the Breslow Intermediate, but as a nucleophile in the following Michael addition step. In fact, the enolizable α-carbon atom in the aza-benzoin product results a stronger nucleophilic site compared to the contiguous nitrogen atom and reacts in the Michael addition furnishing exclusively the dihydroindenone derivative.

Bode developed a cascade sequence involving an aza-benzoin/oxy-Cope strategy for the synthesis of bicyclic α-lactams with diastereoisomeric ratio higher than 10:1 and enantioselectivities up to 98%. The starting reactants included both 3-alkyl or 3-arylenals and chalcone-derived sulfonyl imine (Scheme 26) [40].



Scheme 26. Selected examples of Bode and co-workers synthesis of bicycle-lactams.

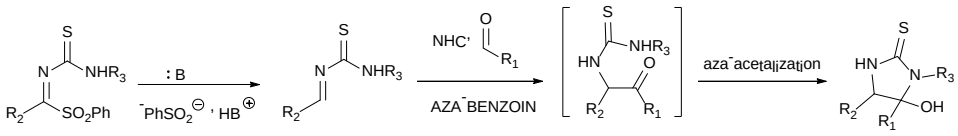
Strictly related to the one-pot processes reviewed in this section is a paper dealing with the addition of homoenolate equivalents to appropriate imines followed by cyclization steps generating γ-lactams (Scheme 27) [41].



Scheme 27. Selected examples of Bode and co-workers catalytic synthesis of lactams.

Disubstituted γ-lactams with high diastereoselectivity have been obtained in the reaction of a series of cinnamaldehydes with electron-rich N-sulfonyl imines in the presence of precatalyst **I-14**.

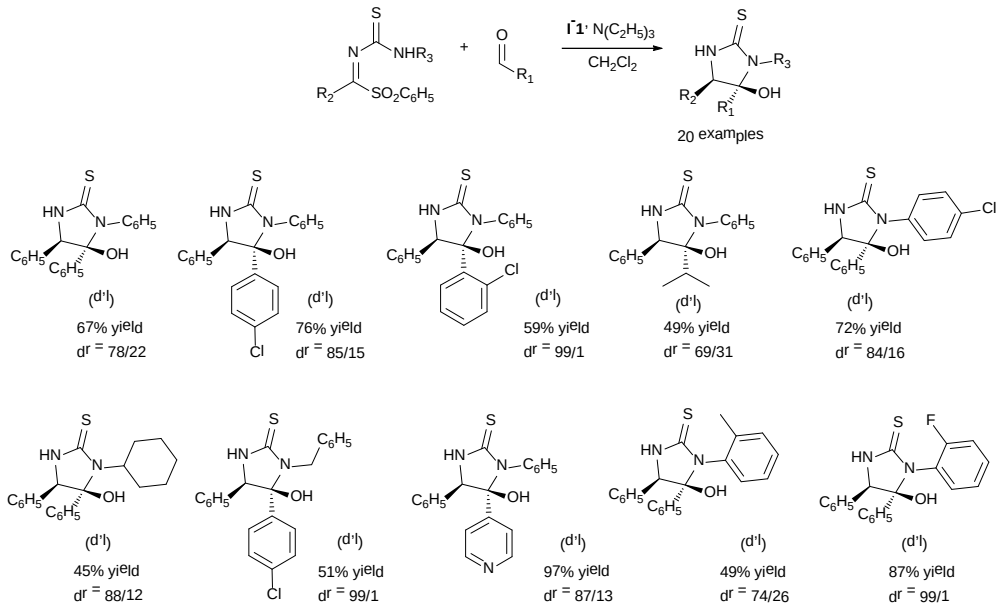
Novel acyl anion acceptors, namely benzylidene thio-ureas, have been used in a domino aza-benzoin/intermolecular aza-acetalization process for the synthesis of 5-hydroxy-imidazolidene-2-thiones, a class of heterocycles displaying relevant biological activities (Scheme 28) [42].



Scheme 28. Strategy for the synthesis of 5-hydroxy-imidazolidene-2-thiones.

The generality of the strategy toward imidazolidine-2-thiones was investigated by considering variations on the structures of both the aromatic aldehydes and the α-sulfonyl amines (Scheme 29).

Further studies demonstrated that the novel cyclization reaction could be run under optimized conditions on a large scale without losing reactivity or diastereoselectivity.



1.2 equiv of aldehyde, 20 mol% of precatalyst, 3 equiv of TEA, CH_2Cl_2 and MeOH, 4A MS, 30 °C, 16 h.

Scheme 29. Bortolini and co-workers selected examples of the one-pot synthesis of 5-hydroxy-imidazolidene-2-thiones.

6. A successful application of aza-benzoin condensation to the synthesis of a pharmaceutical candidate

Metabotropic Glutamate Receptors 5 (mGluR5) are broadly expressed throughout the central nervous system and are implicated in different cognitive and behavioural processes. The molecule depicted in Figure 4 has been identified as a potential candidate for pre-clinical development of mGluR5 modulators [43].

tert-Butyl or benzyl ((*1R,2S*)-1-(5-bromo pyridin-3-yl)-2-(2,5-difluorophenyl)-2-hydroxyethyl) carbamate have been selected as the key intermediate for the synthesis of the target mGluR5 modulator. Unfortunally, their preparation *via* aminohydroxylation occurs with low regioselectivity.

The resolutive approach has been envisaged in the asymmetric reduction of a protected α-aminoketone assembled by a regioselective aza-benzoin condensation catalysed by **I-1**.

The same approach could be applied for the synthesis of other 1,2-amino alcohols, were the traditional methods based on functionalization of alkenes may suffer from selectivity issues.

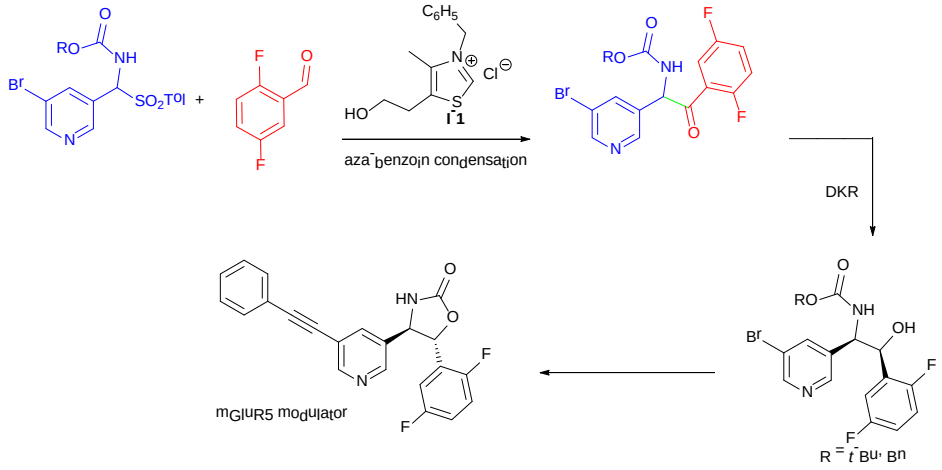


Figure 4. Synthetic approach through the aza-benzoin reation for the preparation of mGluR5 modulator.

7. Conclusions

The aza-benzoin condensation represents a useful enrichment of organic chemistry tools complementary to the traditional cross benzoin reaction.

The different electrophilicity of imines with respect to aldehydes and the possibility to further tune their reactivity by a careful choice of the protecting group on the nitrogen atom, offers the possibility to solve the problem of chemoselectivity which represents the weak point of the cross benzoin coupling between two different aldehydes. For this reason, the aza-benzoin condensation allows an easy access in a regioselective manner to valuable α-amino ketones. The possibility to take advantage of a great number of structurally different chiral N-heterocyclic carbenes has successful improved stereoselective protocols which have provided α-amino ketones with high enantiomeric excesses. Moreover, the experimental requirements consent to include the aza-benzoin condensation in domino processes for the straightforward synthesis of complex cyclic derivatives. In conclusion, the aza-benzoin reaction is a general, practical and broad scope methodology which forebodes new interesting developments.

Author Contributions: Domenico C. M. Albanese and Nicoletta Gaggero wrote the paper.

Conflicts of Interest: "The authors declare no conflict of interest."

References

1. Carroll, F.I.; Blough, B.E.; Mascarella, S.W.; Navarro, H.A.; Eaton, J.B.; Lukas, R.J.; Damaj, M.I. Synthesis and biological evaluation of bupropion analogues as potential pharmacotherapies for smoking cessation. *J. Med. Chem.*, **2010**, *53*, 2204-2214. DOI: 10.1021/jm9017465.
2. Besse, P.; Veschambre, H.; Dickman M.; Chenevert, R. Enantioselective synthesis of both enantiomers of cathinone via the microbiological reduction of 2-azido- 1-phenyl- 1-propanone *J. Org. Chem.*, **1994**, *59*, 8288-8291. DOI: 10.1021/jo00105a060
3. Tao, J.; Hu, S.; Tian, Q.; Nayyar N.; Babu, S. Chemoenzymatic synthesis of ketomethylene tripeptide isosteres. *Tetrahedron: Asymmetry*, **2005**, *16*, 699-703. DOI: 10.1016/j.tetasy.2004.11.092.

4. Miyake, F.; Hashimoto, M.; Tonsiengsom, S.; Yakushijin K.; Horne, D.A. Synthesis of 5-(3-indolyl)oxazole natural products. Structure revision of Almazole D. *Tetrahedron*, **2010**, *66*, 4888-4893. DOI: 10.1016/j.tet.2010.03.109.
5. Ager, J.; Prakash I.; Schaad, D. R. 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem. Rev.*, **1996**, *96*, 835-876. DOI: 10.1021/cr9500038.
6. Lucet, D.; Le Gall T.; Mioskowski, C. The chemistry of vicinal diamines. *Angew. Chem. Int. Ed.*, **1998**, *37*, 2580-2627. DOI: 10.1002/(SICI)1521-3773(19981016)37:19<2580::AID-ANIE2580>3.0.CO;2-L.
7. Adam, I.; Orain D.; Meier, I. Concise synthesis of 1*H*-pyrazin-2-ones and 2-aminopyrazines. *Synlett.* **2004**, 2031-2033. DOI: 10.1055/s-2004-830866.
8. Bodtke, A.; Pfeiffer, W.D.; Goerls, H.; Dollinger H.; Langer, P. Synthesis of 5-thioxo-6*H*-imidazo [1,2-*c*]quinazolines and related compounds based on cyclocondensations of 2-isothiocyanato benzonitrile (ITCB) with α-aminoketones. *Tetrahedron*, **2007**, *63*, 11287-11298. DOI: 10.1016/j.tet.2007.08.090.
9. Bunescu, A.; Piemontesi, C.; Wang Q.; Zhu, J. Heteroannulation of arynes with N-aryl-α-amino ketones for the synthesis of unsymmetrical N-aryl-2,3-disubstituted indoles: an aryne twist of Bischler-Möhlau indole synthesis. *Chem. Commun*., **2013**, *49*, 10284-10286. DOI: 10.1039/C3CC46361C.
10. Mao, Z.; Qu, H.; Zhao Y.; Lin, X. A general access to 1,1-cyclopropane aminoketones and their conversion into 2-benzoyl quinolones. *Chem. Commun*., **2012**, *48*, 9927-9929. DOI: 0.1039/c2cc35235d.
11. Belot, S.; Sulzer-Mosse, S.; Kehrli S.; Alexakis, A. Enantioselective organocatalytic conjugate addition of α-aminoketone to nitroolefins. *Chem. Commun*., **2008**, *39*, 4694-4696. 10.1039/B810789K.
12. Concellon, J.M.; Rodriguez-Solla, H. Synthesis and synthetic applications of α-amino ketones derived from natural α-amino acids. *Curr. Org. Chem*., **2008**, *12*, 524-543. DOI: 10.2174/138527208784245996.
13. Patonay, T.; Kónyaa K.; Juhász-Tótha, É. Syntheses and transformations of α-azido ketones and related derivatives. *Chem. Soc. Rev*., **2011**, *40*, 2797-2847. DOI: 10.1039/C0CS00101E.
14. Ballini, R.; Bosica, G.; Fiorini D.; Palmieri, A. Acyclic α-nitro ketones: a versatile class of α-functionalized ketones in organic synthesis. *Tetrahedron*, **2005**, *61*, 8971-8993. DOI: doi.org/10.1016/j.tet.2005.06.033.
15. Conrad, K.; Hsiao, Y.; Miller, R. A practical one-pot process for α-amino aryl ketone synthesis. *Tetrahedron Lett*., **2005**, *46*, 8587-8589. DOI: doi.org/10.1016/j.tetlet.2005.09.183.
16. Castells, J.; López-Calahorra, F.; Bassedas M.; Urrios, P. A new thiazolium salt-catalyzed synthesis of α-aminoketones from aldehydes and iminium salts. *Synthesis*, **1988**, 314-315. DOI: 10.1055/s-1988-27552.
17. Flanigan, D.M.; Romanov-Michailidis, F.; White, N.A.; Rovis, T. Organocatalytic reactions enabled by N-heterocyclic carbenes. *Chem. Rev*., **2015**, *115*, 9307-9387. DOI: 10.1021/acs.chemrev.5b00060.
18. Wilde M.M.D.; Gravel, M. Bis(amino)cyclopropenylidene (BAC) catalyzed aza-benzoin reaction. *Org. Lett*., **2014**, 16, 5308-5311. DOI: 10.1021/ol5024807.
19. Petrini M.; Torregiani, E. Recent advances in stereoselective syntheses using N-acylimines. *Synthesis*, **2007**, 159-186. DOI: 10.1055/s-2006-958957.
20. Friestad G.K.; Mathies, A.K. Recent developments in asymmetric catalytic addition to C=N bonds. *Tetrahedron*, **2007**, 63, 2541-2569. DOI: 10.1016/j.tet.2006.11.076.
21. Ferraris, D. Catalytic, asymmetric alkylation of imines. *Tetrahedron*, **2007**, 63, 9581-9597. DOI: 10.1016/j.tet.2007.06.043.
22. Gaggero N.; Pandini, S. Advances in chemoselective intermolecular cross-benzoin-type condensation reactions. *Org. Biomol. Chem.*, **2017**, *15*, 6867-6887 and references cited therein. DOI: 10.1039/C7OB01662J.
23. DiRocco D.A.; Rovis, T. Catalytic asymmetric cross-aza-benzoin reactions of aliphatic aldehydes with N-Boc-protected Imines. *Angew. Chem. Int. Ed*., **2012**, *51*, 5904-5906. DOI: 10.1002/anie.201202442.
24. DiRocco, D.A.; Oberg K. N. ; Rovis, T. Isolable analogues of the Breslow Intermediate derived from chiral triazolylidene carbenes. *J. Am. Chem. Soc*., **2012**, *134*, 6143-6145. DOI: 10.1021/ja302031v.
25. He M.; Bode, J.W. Catalytic synthesis of ɣ-lactams via direct annulations of enals via N-sulfonylimines. *Org. Lett.* **2005**, *7*, 3131-3134. DOI: 10.1021/ol051234w.
26. Murry, J.A.; Frantz, D.E.; Soheil, A.; Tillyer R.; Grabowski E.J.J.; Reider, J.P. Synthesis of α-amido ketones via organic catalysis: thiazolium-catalyzed cross-coupling of aldehydes with acylimines. *J. Am. Chem. Soc*., **2001**, *123*, 9696-9697. DOI: 10.1021/ja0165943.

27. Frantz, D.E.; Morency, L.; Soheili, A.; Murry, J:A; Grabowski E.J.J.; Tillyer, R.D. Synthesis of substituted imidazoles via organocatalysis. *Org. Lett*., **2004**, *6*, 843-846. DOI: 10.1021/ol0498803.
28. Li, G.Q.; Dai, L.X.; You, S.L. Thiazolium-derived N-heterocyclic carbene-catalyzed cross-coupling of aldehydes with unactivated imines. *Chem. Commun*., **2007**, 852-854. 10.1039/B611646A.
29. Brook, A.G. Triphenylsilyl Phenyl Ketone. *J. Am. Chem. Soc*., **1957**, *79*, 4373-4375. DOI: 10.1021/ja01573a036.
30. Mattson A.E.; Scheidt, K.A. Catalytic additions of acylsilanes to imines: an acyl anion strategy for the direct synthesis of α-amino ketones. *Org. Lett*., **2004**, *6*, 4363-4366. DOI: 10.1021/ol0481129.
31. Enders, D.; Henseler, A.; Lowins, S. N-Heterocyclic carbene catalyzed nucleophilic acylation of trifluoromethyl Ketimines. *Synthesis*, **2009**, 4125-4128. DOI: 10.1055/s-0029-1217070.
32. Wilde, M.M.D.; Gravel, M. Bis(amino)cyclopropenylidenes as organocatalysts for acyl anion and extended umpolung reactions. *Angew. Chem. Int. Ed*., **2013**, *52*, 12651-12654. DOI: 10.1002/anie.201307167.
33. Ramanjaneyulu, B.T.; Mahesh S.; Anand, R.V. Bis(amino)cyclopropenylidene-catalyzed 1,6-conjugate addition of aromatic aldehydes to *para*-quinone methides: expedient access to *α,α′*-diarylated ketones. *Org. Lett*., **2015**, *17*, 3952-3955. DOI: 10.1021/acs.orglett.5b01724.
34. Mennen, S.M.; Gipson, J.D.; Kim Y.R.; Miller, S.J. Thiazolylalanine-derived catalysts for enantioselective intermolecular aldehyde-imine cross-couplings. *J. Am. Chem. Soc*., **2005**, *127*, 1654-1655. DOI: 10.1021/ja042650z.
35. Sun, L.H.; Liang, Z.Q.; Jia, W.Q.; Ye, S. Enantioselective N-heterocyclic carbene catalyzed aza-benzoin reaction of enals with activated ketimines. *Angew. Chem. Int. Ed*., **2013**, *52*, 5803-5306. DOI: 10.1002/anie.201301304.
36. Xu, J.; Mou, C.; Zhu, T.; Song B.-A.; Chi, Y.R. N-Heterocyclic carbene-catalyzed chemoselective cross-aza-benzoin reaction of enals with isatin-derived ketimines: access to chiral quaternary aminooxindoles. *Org. Lett*. **2014**, *16*, 3272-3275. DOI: 10.1021/ol501286e.
37. Peng, Q.; Guo, D.; Bie, J.; Wang, J. Catalytic enantioselective aza-benzoin reactions of aldehydes with 2*H*-azirines. *Angew. Chem. Int. Ed*. **2018**, *57*, 3767 –3771
38. Sun, F.-g.; Ye, S. N-Heterocyclic carbene-catalyzed [4 + 1] annulation of phthalaldehyde and imines. *Org. Biomol. Chem*., **2011**, *9*, 3632-3635. DOI: 10.1039/C1OB05092C.
39. Wu, K.-J.; Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. N-Heterocyclic carbene-catalyzed tandem aza-benzoin/Michael reactions: on site reversal of the reactivity of N-Boc imines. *Chem. Commun*. **2011**, *47*, 493-495. DOI: 10.1039/C0CC05557C.
40. He, M.; Bode, J. W. Enantioselective, NHC-catalyzed bicyclo-*β*-lactam formation via direct annulations of enals and unsaturated N-sulfonyl ketimines. *J. Am. Chem. Soc*., **2008**, *130*, 418-419. DOI: 10.1021/ja0778592.
41. He M.; Bode, J. W. Catalytic synthesis of *γ*-lactams via direct annulations of enals and N-sulfonylimines. *Org. Lett*. **2005**, *7*, 3131-3134. DOI: 10.1021/ol051234w.
42. Di Carmine, G.; Ragno, D.; De Risi, C.; Bortolini, O.; Giovannini, P. P.; Fantin, G.; Massi, A. Synthesis of functionalized imidazoline-2-thiones via NHC/base-promoted aza-benzoin/aza-acetalization domino reactions. *Org. Biomol. Chem*., **2017**, *15*, 8788-8801.
43. González-Bobes, F.; Hanson, R.; Strotman, N.; Guo, Z.; Goswamia, A. Enantioselective synthesis of a positive allosteric modulator of the metabotropic glutamate receptor 5 (mGluR5) receptor *via* dynamic kinetic resolution of *a*-amino ketones. *Adv. Synth. Catal*., **2016**, *358*, 2077-2082. DOI: 10.1002/adsc.201600329.

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