Stereoselective conjugate cyanation of enals by combining photoredox and organocatalysis

Stereoselective conjugate cyanation of enals by combining photoredox and organocatalysis

Martin Berger[1†], Dengke Ma[1†], Yann Baumgartner[1†], Thomas Hin-Fung Wong[1], & Paolo Melchiorre[1,2*]

1 – *ICIQ*, Institute of Chemical Research of Catalonia - the Barcelona Institute of Science and Technology, Av. Països Catalans 16 – 43007, Tarragona, Spain.

2 – University of Bologna, Department of Industrial Chemistry *'Toso Montanari'*, viale Risorgimento 4 – 40129, Bologna, Italy.

†These authors contributed equally to this work

*email: p.melchiorre@unibo.it

Precise control over the selectivity of a reaction is a fundamental target. While great advances have been obtained in achieving stereocontrol, the selective manipulation of functional groups within a substrate (chemoselectivity) is still a challenge. The cyanation of aldehydes offers an illustrative example: the 1,2-addition of nucleophilic cyanide to the aldehydic group was one the first examples of a stereoselective catalytic process. In contrast, the conjugate cyanation of linear α,β-unsaturated aldehydes has remained elusive, even in a racemic variant. The main difficulty lies in achieving 1,4 chemoselectivity over the preferred cyanide 1,2-addition. Here, we report an asymmetric catalytic method to achieve the exclusive conjugate cyanation of enals. The synergistic action of a chiral organocatalyst with a visible-light-activated photoredox catalyst promotes the single-electron reduction of enals, inducing a formal inversion of polarity. The resulting chiral radicals, being nucleophilic in character, is then intercepted by an electrophilic cyanide source with perfect 1,4 chemoselectivity and good stereocontrol.

Introduction

The catalytic asymmetric addition of cyanide to carbonyl compounds[1-4] is an organic chemistry classic that has found wide application for the preparation of valuable chiral cyanohydrins.[5,6] Efforts to develop stereoselective variants began with the dawn of enantioselective catalytic synthesis[7,8]. As early as 1912, Bredig and Fiske[9] used an alkaloid-derived organic catalyst to promote the addition of HCN to benzaldehyde (Fig. 1a). Despite its low stereoselectivity (enantiomeric ratio, e.r. < 55:45), this process offered the first example of non-enzymatic asymmetric catalysis developed by chemists[8]. The versatility of the cyanation chemistry was later expanded to the asymmetric conjugate addition to α,β-unsaturated carbonyl compounds, including imides[10,11] and ketones[12-14]. These processes relied on chiral catalysts that could secure complete chemoselectivity for the cyanide 1,4-addition. However, to date the stereoselective conjugate cyanation of α,β-unsaturated aldehydes **1** has remained elusive (Fig. 1a). Racemic examples are also rare and restricted to purposely tailored cyclic substrates[15,16]. The overwhelming preference of enals **1** for reacting with the nucleophilic cyanide at the aldehydic functionality instead of the β-carbon (1,2 *vs* 1,4 chemoselectivity) is a consequence of both electronic and steric factors[17], and was observed at a very early stage. In 1954, Prelog and Wilhelm[18] reinvestigated the pioneering organocatalytic system of Bredig and Fiske[9]. They realised that cinnamaldehyde (R = Ph in Fig. 1a) reacted with HCN with exclusive 1,2-chemoselectivity. All the methodologies reported so far confirmed that linear enals undergo exclusive cyanide 1,2-addition at the carbonyl moiety.[6,19-20]

Herein, we report an initial solution to this longstanding problem, detailing a catalytic method for the asymmetric conjugate cyanation of aliphatic α,β-unsaturated aldehydes proceeding with exclusive 1,4-chemoselectivity[21] (Fig. 1b). The synergistic action of a chiral organic catalyst with a visible-light-activated photoredox catalyst promotes the single-electron transfer (SET) reduction of enals **1**, inducing a formal inversion of polarity. The resulting chiral radicals, being nucleophilic in character, is then intercepted by an electrophilic cyanide source with perfect 1,4 chemoselectivity and good stereocontrol.

Results

Design plan

Our design plan was informed by the notion that classic ionic pathways are not suitable for the conjugate 1,4-cyanation. We therefore considered using a different reactivity, based on radical mechanisms, to achieve the target.

As detailed in Fig. 1b, we sought to apply the iminium ion activation strategy[22] to activate enals **1**. The iminium ion **A**, generated upon condensation of a chiral amine catalyst and **1**, has an electrophilic nature. While **A** has found many applications to facilitate enantioselective conjugate additions of nucleophiles, it has failed to promote the chemoselective 1,4 cyanide addition in the polar domain. We reasoned that the electron-poor nature of iminium ion **A** could be leveraged to access a completely distinct reaction path by facilitating anSET reduction. This step would lead to the formation of a chiral 5π-electron β-enaminyl radical **B**. Intermediate **B** was recently generated from saturated aldehydes through a different mechanism[23], and it was shown to possess a nucleophilic character. This reactivity served to intercept electrophilic substrates, e.g. Michael acceptors, but only in a racemic fashion[24]. We recognised that the ability to generate the 5π-enaminyl radical **B** directly from enals **1** would offer a way to formally reverse the substrate polarity, since the originally electrophilic β-carbon in **1** would become nucleophilic in **B**. This *umpolung* strategy[25] would allow the use of an electrophilic CN source, which could react exclusively with radical **B** while leaving untouched the second electrophilic site in enal **1**, namely the carbonyl group. If successfully combined with a stereocontrolled radical-based C-C bond-forming step, this strategy would offer the first example of asymmetric catalytic conjugate cyanation of enals.

Reaction development and mechanistic proposal

From the outset, we recognised the identification of a suitable electrophilic CN source as crucial to realising our design plan. In 1992, Barton established the ability of the stable and commercially available tosyl cyanide (TsCN) to intercept carbon-centred radicals[26]. The resulting nitrile transfer strategy has found many synthetic applications since then[27,28], but an asymmetric catalytic variant has remained elusive. We sought to use TsCN in an enantioselective manifold to develop the organocatalytic conjugate cyanation of enals. Specifically, we explored the reaction between octenal **1a** and TsCN catalysed by a variety of chiral amine catalysts (Fig. 2a).

Initial experiments were conducted in dimethoxyethane (DME) as solvent under irradiation by a blue LED (λ_{max} = 460 nm, see Supplementary Figure 1 for details of the reaction setup), using the organic photocatalyst ***4-CzIPN***[29] (1 mol%) and dihydropyridine **R-1**[30] as the reductive quencher. To facilitate iminium ion formation and secure a high concentration of this intermediate, an excess of enal **1a** was used (3 equiv.). Chiral secondary amine catalysts **A-1** and **A-2**, with an established ability to promote iminium ion-based processes[22], afforded the target conjugate cyanation product **2a** with poor yield and no stereocontrol (entries 1&2). Pleasingly, the *gem*-difluorinated diarylprolinol silylether catalyst **A-3**, which we recently designed to enable the photo-excitation of aromatic enals[31], offered promising results (entry 3, adduct **2a** formed with exclusive 1,4-selectivity, 67% yield, and 71:29 e.r.). The use of ethyl acetate (EtOAc) as solvent secured a significant increase in stereocontrol (81:19 e.r., entry 4). A final cycle of catalyst optimisation established amine **A-4**, possessing bulkier perfluoro-isopropyl groups on the arene scaffold, as suitable for improving enantiocontrol while preserving the catalytic activity (88:12 e.r., entry 5). Increasing the organocatalyst amount to 30 mol% secured the best results (entry 6, **2a** isolated in 75% yield and 91:9 e.r., single regioisomer). Similar results were obtained using a commercial lamp emitting at 456 nm (see page S19 in the Supplementary Information (SI) for details). Control experiments established the importance of all the reaction components, since no product **2a** formation was observed in the absence of light irradiation, photocatalyst, or amine catalyst (entries 7&8). The nature of the reductive quencher was also important, since Hantzsch ester **R-2**, bearing two hydrogens at the C4 position, drastically reduced the yield of **2a** because of a competitive polar reduction of enal via hydride delivery (entry 9) [32]. In all the productive experiments in Fig. 2a, the sulfone by-product **2a'**, arising from the competitive addition of tosyl radical to enal **1a** (or from the polar addition of the sulfinate generated upon reduction), was formed in a similar amount as the target adduct **2a** (see below for a mechanistic discussion and the Supplementary Methods for details). Products **2a** and **2a'** could be readily separated by chromatography purification upon carbonyl reduction.

Fig. 2b details our proposed mechanism for this stereoselective conjugate cyanation of enals **1**. Upon excitation, photocatalyst 4-CzIPN is quenched by dihydropyridine **R-1** (E^{ox} = +1.37 V vs. Ag/AgCl) to form the reducing species 4-CzIPN$^{\bullet-}$ ($E_{1/2}$(4-CzIPN/4-CzIPN$^{\bullet-}$) = -1.21 V vs SCE)[29], as confirmed by Stern-Volmer quenching studies (see Supplementary Figures 75-81 for details, where we also show the inability of TsCN to quench the photocatalyst). 4-CzIPN$^{\bullet-}$ would then reduce via an SET the electron-poor iminium ion **A**, generated upon condensation of aminocatalyst **A-4** and enal **1**, to afford the chiral β-enaminyl radical **B**. The steric fragment within **B** could then master the interception of TsCN, inferring a high degree of stereo- and β site-selectivity. Upon stereocontrolled nitrile transfer, the ensuing radical **C** undergoes β-fragmentation leading to enamine **D** while releasing the tosyl radical **E**, responsible for the formation of by-product **2'**. Hydrolysis of **D** will then afford the target chiral β-cyanoaldehyde **2** while regenerating the organocatalyst **A-4**.

Scope and application of the methodology

We then evaluated the synthetic potential of the conjugate cyanation adopting the optimised conditions detailed in Fig. 2a, entry 6, and conducting the experiments on a synthetically meaningful scale (0.25 mmol). Fig. 3a details

the enals **1** that can undergo the asymmetric 1,4-cyanation successfully. To facilitate work-up, we isolated the corresponding cyano-alcohols **3**, formed upon $NaBH_4$ reduction of the crude products **2**. We also demonstrated the feasibility of isolating different aldehydic adducts **2** (see below). A wide range of structurally different aliphatic substituents at the β position of enals was tolerated well, with the corresponding β-cyanoaldehydes being formed with perfect β-chemoselectivity and high stereoselectivity (e.r. consistently in the range of 90:10). The lowest level of stereocontrol was achieved with crotonaldehyde (product **3b**, 85:15 e.r.), which is a consequence of the small size of the methyl fragment challenging the chiral catalyst's ability to infer stereoselectivity. Branched enals (products **3c**-**d**) and chains bearing differently substituted aryl fragments were tolerated (**3e**-**3h**). The absolute configuration of a derivative of product **3d**, obtained upon acylation with *p*-nitrobenzoyl chloride, was unambiguously assigned by X-ray crystallographic analysis. The presence of an unsaturation did not lead to undesired side reactions, smoothly affording the corresponding products. Both terminal (adduct **3i**) and internal olefins (**3j** and **3k**) could be reacted. Terminal alkynes were equally tolerated (product **3l**). A large variety of reactive functional groups were compatible with the cyanation conditions, including an imide (product **2m**), an ether functionality (**3n**), a preinstalled nitrile (adduct **3o**), an amide (**2p**), an unprotected alcohol (**2q**), a terminal chloride (**2s**), and an unprotected carboxylic acid (product **2t**). The method was also suitable for the cyanation of a complex steroid derivative adorned with reactive ketone functionalities. The corresponding product **2r** could be isolated smoothly in 9:1 d.r. The latter result, along with the high diastereoselectivity achieved in the cyanation of a citronellal derivative leading to adduct **3j**, established the amine catalyst **A-4** (and not the chiral substrate) as the dominant factor for stereocontrol. The conjugate cyanation of **1a** could be scaled up to 1 mmol scale while affecting efficiency only slightly (product **3a** isolated in 55% yield and 90.5:9.5 e.r.). Finally, we demonstrated the possibility of isolating the β-cyanoaldehyde products for different adducts, including **2m** and **2p**-**r**. As a limitation of the system, enals bearing aromatic β substituents remained completely unreactive. Also an aliphatic α-methyl enone (e.g. (*E*)-non-3-en-2-one) did not react under the optimised conditions.

The conjugate cyanation grants access to difunctional β-cyanoaldehyde adducts **2** that are readily converted to a variety of useful chiral building blocks (Fig. 3b). For example, the preserved aldehyde function in **2a** could be further reacted with classical nucleophilic cyanide. This one-pot 1,4–1,2 double cyanation, which sequentially combined a radical and a polar process, directly led to cyanohydrin **4a** in high yield and good enantiopurity (*path i*). The 1,4-cyanation of **1a**, followed by one-pot Pinnick oxidation, allowed conversion into the β-cyano-carboxylic acid **4b** (*path ii*). Subsequent Pd-catalysed hydrogenation of the nitrile functionality (*path iii*) offered a straightforward entry to biologically valuable γ-aminobutyric acid (GABA) derivative **4c**, which was obtained without erosion of e.r.

Discussion

The main feature of our strategy is to invert the innate reactivity of enals, making their β carbon nucleophilic via the transient formation of the chiral β-enaminyl radical intermediate **B**. We reasoned that this umpolung activation mode could be general and extended to other asymmetric transformations. Accordingly, we successfully developed a chemo- and stereo-selective β-alkylation of enals **1** using acrylates **5** as electrophilic partners (Fig. 4a). The overall process is a cross-electrophile coupling that combines two Michael acceptors to form synthetically challenging linear 1,6-dicarbonyl compounds **6**[33]. Previous methods to directly access chiral acyclic products **6** were not stereocontrolled,[24] while other umpolung strategies that coupled enals with Michael acceptors, based on *N*-heterocyclic carbene organocatalysis[34], could offer cyclic adducts only[35,36].

Using catalyst **A-3** and DME as solvent, our method effectively coupled a variety of enals and *p*-methoxybenzyl (PMB) 2-phenyl acrylate **5**, leading to linear products **6** with exquisite β-selectivity and good enantioselectivity, albeit without control of the relative stereochemistry (see Supplementary Table 1 for details on the optimization). However, the two diastereomeric diols **7a-b** could be readily separated and characterised upon complete reduction of product **6a** by $LiAlH_4$ (Fig. 4b). Owing to the mild reaction conditions, a variety of reactive functional groups within the enal substrate were preserved, including aliphatic (products **6a**-**6d**) and aromatic moieties (**6e**-**6h**), alkenes (adducts **6i**-**6k**), a chloride (**6l**), an unprotected alcohol (**6m**), an ether (**6n**), and an ester moiety (**6o**). Differently substituted acrylates **5** were also suitable coupling partners, leading to the corresponding aldehyde products **6p**-**t** with high yields and good enantiocontrol. The stereochemistry of compound **7e**, the fully reduced descendant of product **6e**, was unambiguously established by X-ray crystallographic analysis of the derivative obtained after acylation with *p*-nitrobenzoyl chloride (Fig. 4c). Finally, we expanded the applicability of the umpolung platform by using allyl sulfone **8**, which served as an effective radical trap (Fig. 4d). The radical addition-desulfonylation process[37] leading to product **9** offered a rare example of the asymmetric catalytic conjugate allylation of enals.

Our strategy is based on the special reactivity of the chiral 5π-enaminyl radical of type **B**, generated upon SET reduction of the iminium ion **A** (Fig. 1b). To unambiguously prove the formation of this crucial intermediate, we performed a reaction using racemic *trans*-(*E*)-3-phenylcyclopropylacrylaldehyde **10** as the substrate, which led to the

formation of product **11** (Fig. 4e). The outcome of the experiment can be reconciled with the tendency of the cyclopropyl fragment within **10** to open up upon formation of 5π-enaminyl radical **F**. Interception of the resulting benzylic radical **G** by acrylate **5a**, followed by 5-*exo*-*trig* cyclisation in **H**, afforded the cyclopentane product **11**.

Conclusion

In conclusion, we have shown how the combination of organocatalysis and photoredox catalysis can be used to address a longstanding problem in the asymmetric synthesis of valuable chiral molecules, providing the first method for the enantioselective conjugate cyanation of α,β-unsaturated aldehydes. We believe that this strategy, which reverses the innate reactivity of enals, is versatile enough to enable the development of other unconventional stereocontrolled radical functionalization processes.

Methods

Representative procedure for the stereoselective conjugate cyanation of enals.

An 8.0 mL vial equipped with a stirring bar was charged with tosyl cyanide (250 µmol, 95% purity, 1.0 equiv.), the chiral amine catalyst **A-4** (75.0 µmol, 0.3 equiv.), dihydropyridine **R-1** (375 µmol, 1.5 equiv.), photocatalyst **4-CzIPN** (2.50 µmol, 1 mol%), and enal **1** (3.0 equiv.). The vial was sealed with a septum and purged with Argon. The reactants were suspended in EtOAc (500 µL, ensure that all compounds are suspended) and deionized water (13.5 µL, 3.0 equiv.) was added. Then, TFA (100 µmol, 0.4 equiv.) was added and the vial was placed in a pre-cooled metal support (set for an internal temperature of 5 °C) mounted on an aluminium block fitted with a high-power single blue LED (λ_{max} = 460 nm, irradiance set at 90 mW/cm² as controlled by an external power supply, see Supplementary Figure 1 for details). After 16 hours of irradiation, the mixture was concentrated under reduced pressure. In case of inseparability of the aldehydic products **2**, reduction of the crude mixture afforded the corresponding alcohols **3**. Analytically pure products **2** or **3** were obtained upon purification by flash column chromatography. Enantiomeric ratios were determined by UPC² analysis upon derivatization of the products (see Supplementary Methods for details).

Representative procedure for the stereoselective cross-electrophile coupling of enals 1 and acrylates 5.

To a 8.0 mL argon-purged glass vial, containing acrylate **5** (1.0 equiv.), enal **1** (3.0 equiv.), **R-1** (375 µmol, 1.5 equiv.), **4-CzIPN** (2.50 µmol, 1 mol%), and amine catalyst **A-3** (50.0 µmol, 20 mol%), was added 500 µL of dimethoxyethane, H_2O (2.50 mmol, 10 equiv.) and TFA (75.0 µmol, 30 mol%). The vial was sealed with Parafilm, and then placed into a cooled aluminium support mounted on an aluminium block fitted with a 460 nm high-power single LED (λ = 460 nm, irradiance = 90 mW/cm², as controlled by an external power supply). The reaction was stirred under visible light irradiation at -10 °C internal temperature for 16 hours. Then the solvent was evaporated, and the crude mixture purified by column chromatography on silica gel to furnish products **6**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric ratios were determined upon derivatization of the products and separation of diastereomers by UPC² analysis.

Data availability Materials and methods, experimental procedures, useful information, mechanistic studies, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request. Crystallographic data for the acylated derivatives of compounds **3d** and **7e** have been deposited with the Cambridge Crystallographic Data Centre, accession numbers CCDC 2197381 and 2197380, respectively.

Acknowledgements Financial support was provided by MCIN AEI/10.13039/501100011033 (CEX2019-000925-S) and Agencia Estatal de Investigación (PID2019-106278GB-I00). M.B. thanks the Austrian Science Fundation (FWF, J4603-N) for an Erwin-Schrödinger postdoctoral fellowship. Y.B. thanks the Swiss National Science Foundation (P2BSP2_200098) for a postdoctoral fellowship. D.M. thanks the EU for a Horizon 2020 Marie Skłodowska-Curie Fellowship (H2020-MSCA-IF-2019 894795). T.H.F.W. thanks the Government of Catalonia for an FI Fellowship (2021FI–B00304). The authors thank Dr. Pietro Capurro for preliminary investigations, Dr. Marta Martinez and Dr. Jordi Benet for X-ray crystallographic analysis, and Dr. Marta Giménez and Cristina Rivero for assistance with ozonolysis and hydrogenation experiments.

Author contributions M.B., Y.B., and T.H.F.W. developed the reaction, investigated the substrate scope, and studied the reaction mechanism. D.M. first observed the reactivity and performed the initial screening. All authors contributed to the experimental design and the interpretation of data. P.M. conceived and supervised the project. M.B., Y.B., and P.M. directed the project. M.B. and P.M. wrote the manuscript with input from all authors.

Competing interests The authors declare no competing interests.

Figure legends/caption

Figure 1 | Asymmetric catalytic cyanation of aldehydes and their unsaturated counterparts. a, Pioneering studies using the classic polar nucleophilic reactivity of cyanide, leading to exclusive 1,2-addition products. **b,** Design plan for reversing the polarity of enals **1** (*umpolung*) and achieving 1,4-chemoselectivity: SET reduction of the electrophilic iminium ion **A** leads to the chiral radical **B** with a nucleophilic character, thus enabling the selective trap of an electrophilic CN source at the β carbon; the grey circle represents the chiral organic catalyst scaffold; SET, single-electron transfer.

Figure 2 | Initial explorations and mechanistic proposal. a, Optimisation studies and identification of the target cyanation product **2a** and by-product **2a'**; reactions performed on a 0.1 mmol scale under illumination by a blue LED; yields determined by ^{1}H NMR analysis using trichloroethylene as the internal standard. **b,** Proposed mechanism for the chemoselective conjugate cyanation of enals by merging the action of photocatalyst 4-CzIPN and chiral amine catalyst **A-4**. *Data in parentheses refer to yield of isolated product upon **2a** reduction; TDS, thexyl-dimethylsilyl.

Figure 3 | Organocatalytic asymmetric conjugate cyanation of enals. a, Enals that can participate in the process; reactions performed on a 0.25 mmol scale. Products isolated as cyanoaldehydes **2** or cyanoalcohols **3** upon one-pot $NaBH_4$ reduction of crude **2** ($NaBH_4$ in THF/water 4:1, 0 °C, 1.5 h); for cyanoalcohols **3**, yields are given over 2 steps (analytical yields of cyanoaldehydes **2** are given in parentheses); *analytical yields are given for products **2s** and **2t**, as inferred by ^{1}H NMR analysis, since they could not be isolated. **b,** Synthetic versatility of cyanoaldehyde **2a** and its straightforward modification to access cyanohydrin **4a** (*path i*), cyanoacid **4b** (*path ii*) en route to GABA derivative **4c** (*path iii*).

Figure 4 | Generality of the umpolung strategy of enals and mechanistic considerations. a, Organocatalytic cross-electrophile coupling leading to chiral 1,6-dicarbonyl compounds **6**; reactions performed on a 0.25 mmol scale; the e.r. values for both diastereomers of **6** are reported. **b,** Separation and isolation of diastereoisomers as diols. **c,** Determination of product configuration. **d,** Organocatalytic asymmetric conjugate allylation of enal. **e,** Mechanistic experiment confirming the transient formation of the 5π-enaminyl radical intermediate **F**. PMB, *p*-methoxybenzyl; TCA, trichloroacetic acid.

References

1. Kurono, N. & Ohkuma, T. Catalytic asymmetric cyanation reactions. *ACS Catal.* **6**, 989–1023 (2016).
2. Reetz, M. T., Kunisch, F. & Heitmann, P. Chiral Lewis acids for enantioselective C-C bond formation. *Tetrahedron Lett.* **27**, 4721–4724 (1986).
3. Zuend, S. J., Coughlin, M. P., Lalonde, M. P. & Jacobsen, E. N. Scalable catalytic asymmetric Strecker syntheses of unnatural α-amino acids. *Nature* **461**, 968–970 (2009).
4. Zhou, H., Zhou, Y., Bae, H. Y., Leutzsch, M., Li Y., De, C. K., Cheng, G.-J. & List, B. Organocatalytic stereoselective cyanosilylation of small ketones. *Nature* **605**, 84–89 (2022).
5. Gregory, R. J. Cyanohydrins in nature and the laboratory: biology, preparations, and synthetic applications. *Chem. Rev.* **99**, 3649–3682 (1999).
6. Zeng, X.-P., Sun, J.-C., Liu, C-, Ji, C.-B. & Peng Y.-Y. Catalytic asymmetric cyanation reactions of aldehydes and ketones in total synthesis. *Adv. Synth. Catal.* **361**, 3281–3305 (2019).
7. Rosenthaler, L. Durch Enzyme bewirkte asymmetrische Synthesen. *Biochem. Z.* **14**, 238–253 (1908).
8. Kagan, H. B. *Historical perspectives*, in *Comprehensive Asymmetric Catalysis*, ed. Jacobsen, E. N., Pfaltz A. & Yamamoto, H. Springer-Verlag, Berlin, vol. 1, p. 4-22 (1999).
9. Bredig, G. & Fiske, P. S. Beiträge zur chemischen Physiologie und Pathologie. *Biochem. Z.* **46**, 7 (1912).
10. Sammis, G. M. & Jacobsen, E. N. Highly enantioselective, catalytic conjugate addition of cyanide to α,β-unsaturated imides. *J. Am. Chem. Soc.* **125**, 4442-4443 (2003).
11. Sammis, G. M., Danjo, H. & Jacobsen, E. N. Cooperative dual catalysis: application to the highly enantioselective conjugate cyanation of unsaturated imides. *J. Am. Chem. Soc*. **126**, 9928–9929 (2004).
12. Tanaka, Y., Kanai, M. & Shibasaki, M. A catalytic enantioselective conjugate addition of cyanide to enones. *J. Am. Chem. Soc.* **130**, 6072–6073 (2008).

13. Tanaka, Y., Kanai, M. & Shibasaki, M. Catalytic enantioselective construction of β-quaternary carbons via a conjugate addition of cyanide to β,β-disubstituted α,β-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **132**, 8862–8863 (2010).
14. Provencher B. A., Bartelson K. J., Liu, Y., Foxman, B. M. & Deng, L. Structural study-guided development of versatile phase-transfer catalysts for asymmetric conjugate additions of cyanide. *Angew. Chem. Int. Ed.* **50**, 10565–10569 (2011).
15. Ito, Y., Kato, H., Imai, H. & Saegusa, T. A novel conjugate hydrocyanation with $TiCl_4$-tert-butyl isocyanide. *J. Am. Chem. Soc.* **104**, 6449–6450 (1982).
16. Jansen, B. J. M., Sengers, H. H. W. J. M., Bos, H. J. Y. & de Groot, A. A new stereoselective approach for the total synthesis of (±)-Isotadeonal, (±)-Polygodial, (±)-Warburganal, and (±)-Muzigadial. *J. Org. Chem*. **53**, 855–859 (1988).
17. Nagata, W. & Yoshioka, M. *Hydrocyanation of conjugated carbonyl compounds* in *25th Organic Reactions*, eds. Dauben, W. G. *et al.*, John Wiley & Sons, Inc. (1977), pp 255–476.
18. Prelog, V. & Wilhelm, M. Untersuchungen über asymmetrische Synthesen VI). Der Reaktionsmechanismus und der sterische Verlauf der asymmetrischen Cyanhydrin-synthese. *Helv. Chim. Acta* **37**, 1634–1660 (1954).
19. Hayashi, M., Miyamoto, Y., Inoue, T. & Oguni, N. Enantioselective trimethylsilylcyanation of some aldehydes catalyzed by chiral Schiff base-titanium alkoxide complexes. *J. Org. Chem.* **58**, 1515–1522 (1993).
20. Hamashima, Y., Sawada, D., Kanai, M. & Shibasaki, M. A new bifunctional asymmetric catalysis: an efficient catalytic asymmetric cyanosilylation of aldehydes. *J. Am. Chem. Soc.* **121**, 2641–2642 (1999).
21. Shenvi, R. A., O'Malley, D. P. & Baran, P. S. Chemoselectivity: the mother of invention in total synthesis. *Acc. Chem. Res.* **42**, 530–541 (2009).
22. Lelais, G. & MacMillan, D. W. C. Modern strategies in organic catalysis: the advent and development of iminium activation. *Aldrichim. Acta* **39**, 79–87 (2006).
23. Pirnot, M. T., Rankic, D. A., Martin, D. B. C. & MacMillan, D. W. C. Photoredox activation for the direct β-arylation of ketones and aldehydes. *Science* **339**, 1593–1596 (2013).
24. Terrett, J. A., Clift, M. D. & MacMillan, D. W. C. Direct β-alkylation of aldehydes via photoredox organocatalysis. *J. Am. Chem. Soc.* **136**, 6858–6861 (2014).
25. Seebach, D. Methods of reactivity umpolung. *Angew. Chem. Int. Ed. Eng.* **18**, 239–258 (1979).
26. Barton, D. H. R., Jaszberenyl, J. C. & Theodorakis, E. A. The invention of radical reactions. Part XXIII new reactions: Nitrile and thiocyanate transfer to carbon radicals from sulfonyl cyanides and sulfonyl isothiocyanates. *Tetrahedron* **48**, 2613–2626 (1992).
27. Gaspar, B. & Carreira, E. M. Mild Cobalt-Catalyzed Hydrocyanation of Olefins with Tosyl Cyanide. *Angew. Chem. Int. Ed*. **46**, 4519–4522 (2007).
28. Ren, R., Wu, Z., Xu, Y. & Zhu, C. C-C Bond-Forming Strategy by Manganese-Catalyzed Oxidative Ring-Opening Cyanation and Ethynylation of Cyclobutanol Derivatives. *Angew. Chem. Int. Ed.* **55**, 2866–2869 (2016).
29. Shang,T.-Y., Lu, L.-H., Cao, Z., Liu, Y., He, W.-H. & Yu, B. Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) in photocatalytic transformations. *Chem. Commun.* **55**, 5408–5419 (2019).
30. Stradins, J., Baumane, L., Kalnins, A., Uldrikis, J., Bisenieks, E., Poikans, J. & Duburs, G. Special Features of the Electrochemical Oxidation of Substituted 4-Carboxy-1,4-dihydropyridines. *Chem. Heterocycl. Compd.* **36**, 1177–1184 (2000).
31. Silvi, M., Verrier, C., Rey, Y. P., Buzzetti, L. & Melchiorre, P. Visible-light excitation of iminium ions enables the enantioselective catalytic β-alkylation of enals. *Nat. Chem.* **9**, 868–873 (2017).
32. Yang, Y. W., Hechavarria Fonseca, M. T. H. & List, B. A Metal-Free Transfer Hydrogenation: Organocatalytic Conjugate Reduction of α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed*. **43**, 6660–6662 (2004).
33. Suresh, R., Massad, I. & Marek, I. Stereoselective tandem iridium-catalyzed alkene isomerization-cope rearrangement of ω-diene epoxides: efficient access to acyclic 1,6-dicarbonyl compounds *Chem. Sci*. **12**, 9328–9332 (2021).
34. Hopkinson, M., Richter, C., Schedler, M. & Glorius, F. An overview of *N*-heterocyclic carbenes. *Nature* **510**, 485–496 (2014).
35. Chiang, P.-C., Kaeobamrung, J. & Bode, J. W. Enantioselective, Cyclopentene-Forming Annulations via NHC-Catalyzed Benzoin−Oxy-Cope Reactions. *J. Am. Chem. Soc.* **129**, 3520–3521 (2007).
36. Cardinal-David, B., Raup, D. E. A. & Scheidt, K. A. Cooperative N-Heterocyclic Carbene/Lewis Acid Catalysis for Highly Stereoselective Annulation Reactions with Homoenolates. *J. Am. Chem. Soc.* **132**, 5345–5347 (2010).
37. Huang, X., Luo, S., Burghaus O., Webster, R. D., Harmsa, K. & Meggers, E. Combining the catalytic enantioselective reaction of visible-light-generated radicals with a byproduct utilization system. *Chem. Sci.* **8**, 7126–7313 (2017).

Author information Correspondence and requests for materials should be addressed to P.M. (p.melchiorre@unibo.it).

Supplementary Information is linked to the online version of the paper.

Figure 1

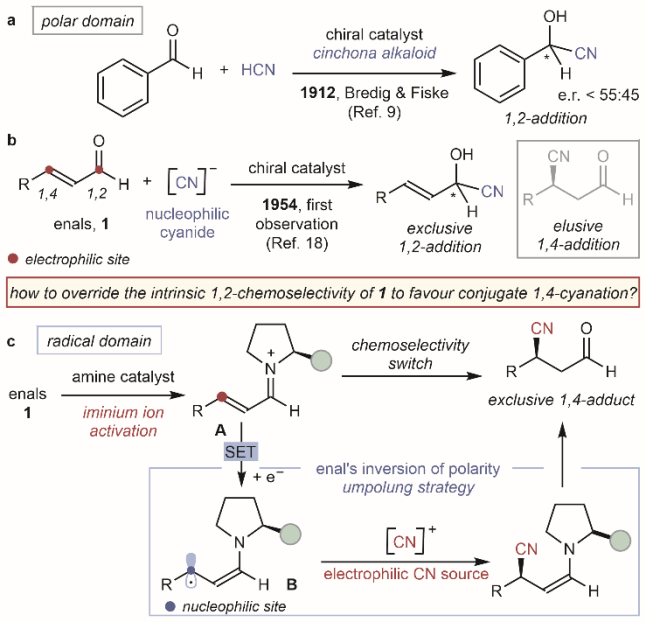
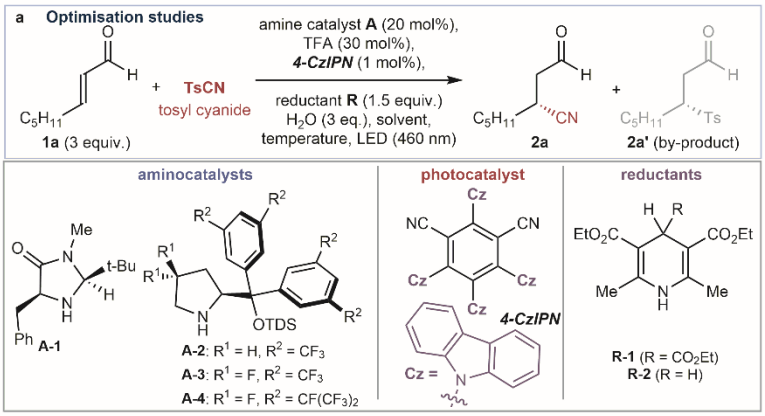


Figure 2



entry	amine **A**	reductant **R**	notes	solvent	T (°C)	**2a** yield (%)	e.r.
1	**A-1**	**R-1**	-	DME	-10	20	50:50
2	**A-2**	**R-1**	-	DME	-10	21	52:48
3	**A-3**	**R-1**	-	DME	-10	67	71:29
4	**A-3**	**R-1**	-	EtOAc	-10	63	81:19
5	**A-4**	**R-1**	-	EtOAc	5	56	88:12
6	**A-4**	**R-1**	**A-4** (30 mol%)	EtOAc	5	77 (75)*	91:9
7	**A-4**	**R-1**	no PC or light	EtOAc	5	0	-
8	-	**R-1**	no amine	EtOAc	5	<10	-
9	**A-3**	**R-2**	-	EtOAc	-10	15	-

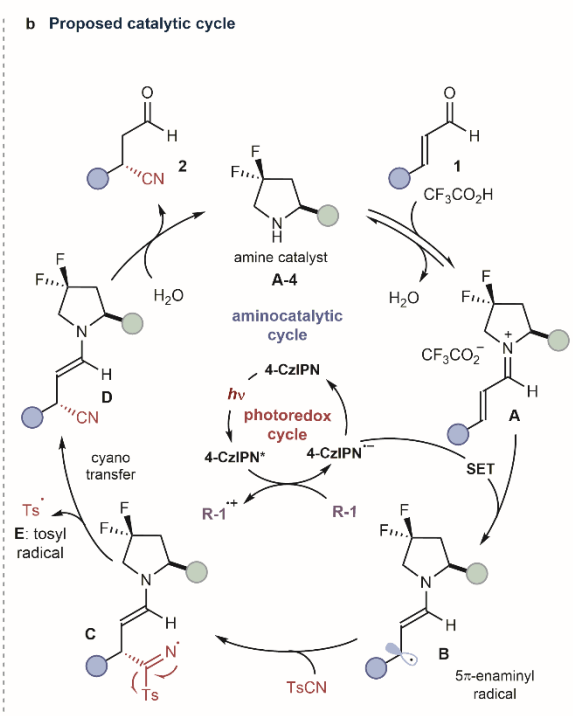


Figure 3

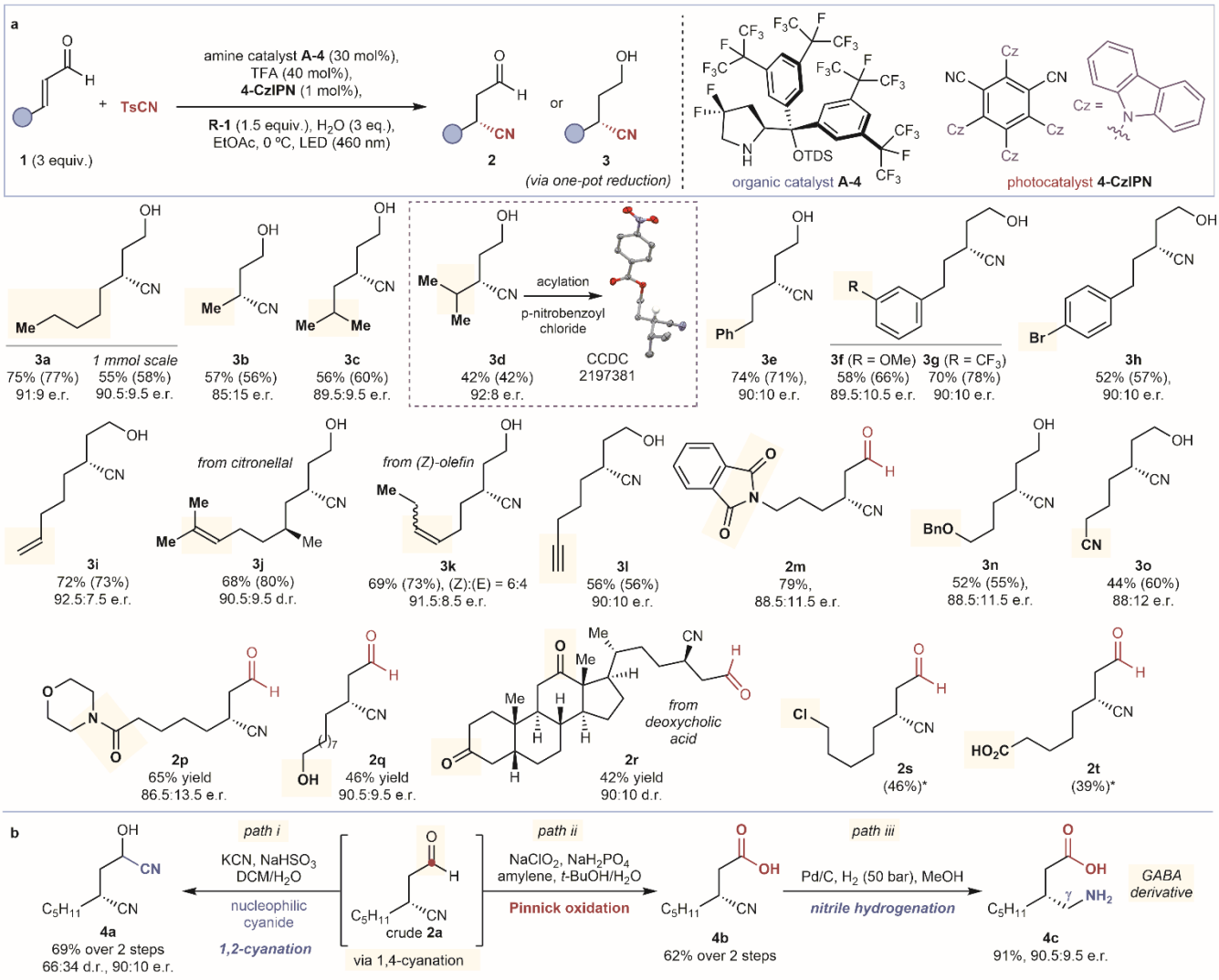
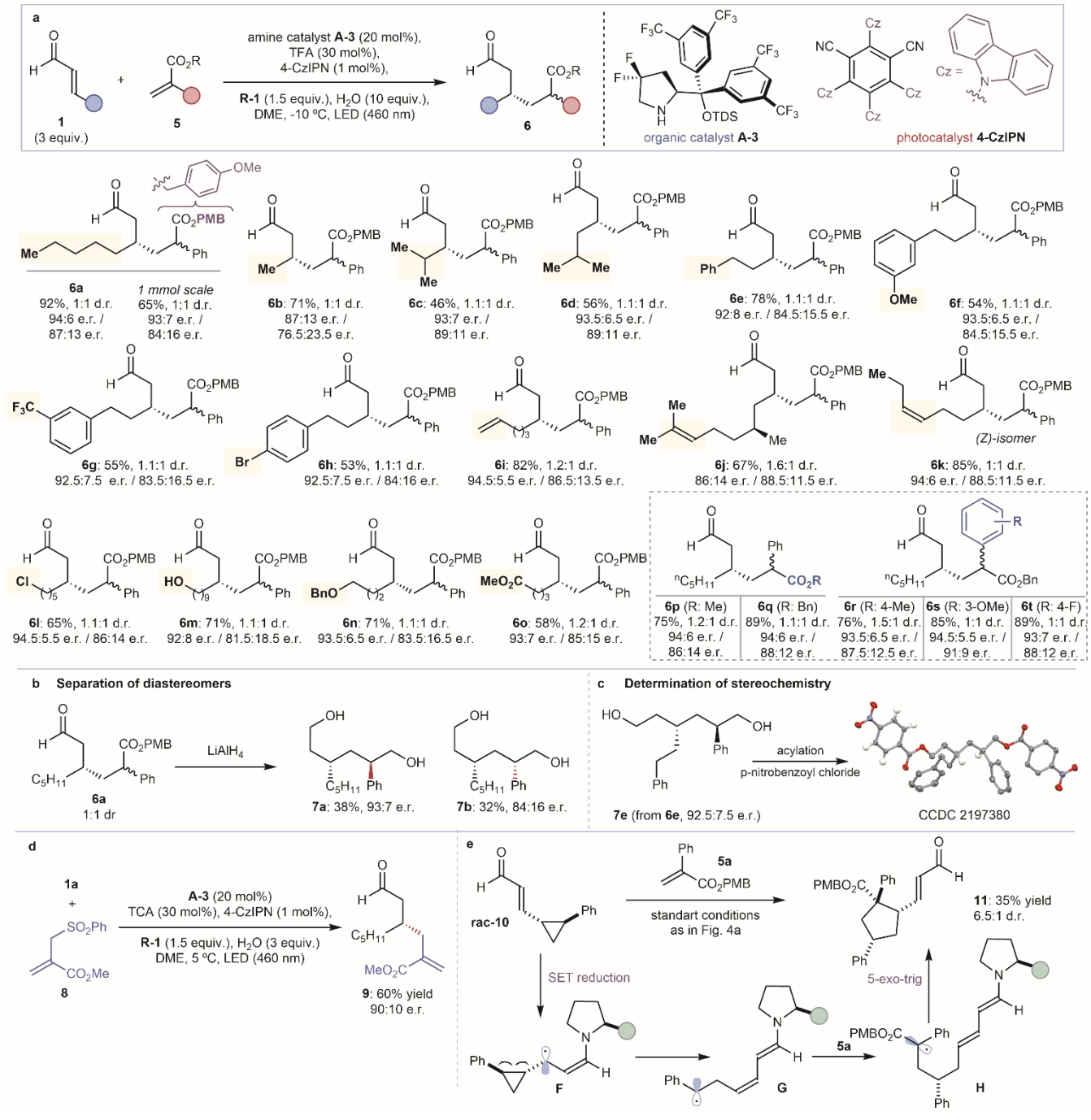

a
1 (3 equiv.)
TsCN
amine catalyst A-4 (30 mol%),
TFA (40 mol%),
4-CzIPN (1 mol%),
R-1 (1.5 equiv.), H2O (3 eq.),
EtOAc, 0 °C, LED (460 nm)
2
or
3
(via one-pot reduction)
organic catalyst A-4
photocatalyst 4-CzIPN
Cz =
3a
1 mmol scale
75% (77%)
91:9 e.r.
55% (58%)
90.5:9.5 e.r.
3b
57% (56%)
85:15 e.r.
3c
56% (60%)
89.5:9.5 e.r.
acylation
p-nitrobenzoyl chloride
3d
42% (42%)
92:8 e.r.
CCDC 2197381
3e
74% (71%),
90:10 e.r.
3f (R = OMe)
58% (66%)
89.5:10.5 e.r.
3g (R = CF3)
70% (78%)
90:10 e.r.
3h
52% (57%),
90:10 e.r.
3i
72% (73%)
92.5:7.5 e.r.
from citronellal
3j
68% (80%)
90.5:9.5 d.r.
from (Z)-olefin
3k
69% (73%), (Z):(E) = 6:4
91.5:8.5 e.r.
3l
56% (56%)
90:10 e.r.
2m
79%,
88.5:11.5 e.r.
3n
52% (55%),
88.5:11.5 e.r.
3o
44% (60%)
88:12 e.r.
2p
65% yield
86.5:13.5 e.r.
2q
46% yield
90.5:9.5 e.r.
from deoxycholic acid
2r
42% yield
90:10 d.r.
2s
(46%)*
2t
(39%)*
b
path i
KCN, NaHSO3
DCM/H2O
nucleophilic cyanide
1,2-cyanation
crude 2a
via 1,4-cyanation
path ii
NaClO2, NaH2PO4
amylene, t-BuOH/H2O
Pinnick oxidation
path iii
Pd/C, H2 (50 bar), MeOH
nitrile hydrogenation
GABA derivative
4a
69% over 2 steps
66:34 d.r., 90:10 e.r.
4b
62% over 2 steps
4c
91%, 90.5:9.5 e.r.

Figure 4


a
amine catalyst A-3 (20 mol%),
TFA (30 mol%),
4-CzIPN (1 mol%),
R-1 (1.5 equiv.), H2O (10 equiv.),
DME, -10 °C, LED (460 nm)
1
(3 equiv.)
5
6
organic catalyst A-3
photocatalyst 4-CzIPN
6a
92%, 1:1 d.r.
94:6 e.r. /
87:13 e.r.
1 mmol scale
65%, 1:1 d.r.
93:7 e.r. /
84:16 e.r.
6b: 71%, 1:1 d.r.
87:13 e.r. /
76.5:23.5 e.r.
6c: 46%, 1.1:1 d.r.
93:7 e.r. /
89:11 e.r.
6d: 56%, 1.1:1 d.r.
93.5:6.5 e.r. /
89:11 e.r.
6e: 78%, 1.1:1 d.r.
92:8 e.r. / 84.5:15.5 e.r.
6f: 54%, 1.1:1 d.r.
93.5:6.5 e.r. /
84.5:15.5 e.r.
6g: 55%, 1.1:1 d.r.
92.5:7.5 e.r. / 83.5:16.5 e.r.
6h: 53%, 1.1:1 d.r.
92.5:7.5 e.r. / 84:16 e.r.
6i: 82%, 1.2:1 d.r.
94.5:5.5 e.r. / 86.5:13.5 e.r.
6j: 67%, 1.6:1 d.r.
86:14 e.r. / 88.5:11.5 e.r.
6k: 85%, 1:1 d.r.
94:6 e.r. / 88.5:11.5 e.r.
(Z)-isomer
6l: 65%, 1.1:1 d.r.
94.5:5.5 e.r. / 86:14 e.r.
6m: 71%, 1.1:1 d.r.
92:8 e.r. / 81.5:18.5 e.r.
6n: 71%, 1.1:1 d.r.
93.5:6.5 e.r. / 83.5:16.5 e.r.
6o: 58%, 1.2:1 d.r.
93:7 e.r. / 85:15 e.r.
6p (R: Me)
75%, 1.2:1 d.r.
94:6 e.r. /
86:14 e.r.
6q (R: Bn)
89%, 1.1:1 d.r.
94:6 e.r. /
88:12 e.r.
6r (R: 4-Me)
76%, 1.5:1 d.r.
93.5:6.5 e.r. /
87.5:12.5 e.r.
6s (R: 3-OMe)
85%, 1:1 d.r.
94.5:5.5 e.r. /
91:9 e.r.
6t (R: 4-F)
89%, 1:1 d.r.
93:7 e.r. /
88:12 e.r.
b Separation of diastereomers
LiAlH4
6a
1:1 dr
7a: 38%, 93:7 e.r.
7b: 32%, 84:16 e.r.
c Determination of stereochemistry
acylation
p-nitrobenzoyl chloride
7e (from 6e, 92.5:7.5 e.r.)
CCDC 2197380
d
1a
A-3 (20 mol%)
TCA (30 mol%), 4-CzIPN (1 mol%),
R-1 (1.5 equiv.), H2O (3 equiv.)
DME, 5 °C, LED (460 nm)
8
9: 60% yield
90:10 e.r.
e
rac-10
5a
standart conditions
as in Fig. 4a
11: 35% yield
6.5:1 d.r.
SET reduction
5-exo-trig
F
G
H