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Asymmetric synthesis of propargylic alcohols *via* aldol reaction of aldehydes with ynals promoted by prolinol ether–transition metal–Brønsted acid cooperative catalysis†

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A catalytic and highly stereoselective entry to propargylic alcohols and products derived thereof is reported based on an unprecedented cross-aldol coupling between unmodified aldehydes and ynals. The method requires an amine–metal salt–Brønsted acid ternary catalyst system and implies synergistic activation of the donor aldehyde *via* enamine and of the acceptor carbonyl *via* unique and reversible metal–alkyne complexation. Specifically, by using a combined α,α-dialkylprolinol silyl ether–CuI–$PhCO_2H$ catalyst system, remarkably high levels of diastereo- and enantioselectivity (*anti*/*syn* up to >20 : 1, ee up to >99%) are achieved.

Introduction

Propargylic alcohols constitute small but densely functionalized units that, owing to the rich chemistry of the carbon–carbon triple bond, may serve as building blocks in the construction of molecular complexity.[1] Despite their synthetic value, there are few catalytic entries to propargylic alcohols of stereodefined structure, namely: (a) the reduction of ynones, (b) the addition of terminal alkynes to aldehydes, and (c) the 1,2-addition of nucleophiles to α,β-ynals (Fig. 1).[2] Although the first two methods have been studied extensively, efforts for exploring the latter approach have been essentially limited to the use of organometallic reagents, which usually allow for the generation of a sole stereocenter and do not readily permit concomitant introduction of additional functionality.

The aldol addition[3] of an enolate or equivalent to an α,β-ynal can be viewed as an attractive means for accessing propargylic alcohols because two contiguous stereocenters may be generated at once, with concomitant formation of a new carbon–carbon bond between them, and a β-carbonyl group is also installed, all under rather mild reaction conditions. However, realizing such a transformation in a catalytic and asymmetric manner from readily available substrates remains poorly addressed, if at all. Here we report a cross aldol reaction between aldehydes and ynals promoted by prolinol ether–transition metal–Brønsted acid cooperative catalysis that enables a straightforward and highly stereocontrolled synthesis of functionalized propargylic alcohols.

Results and discussion

Background and reaction design

Despite the fact that the aldol reaction stands among the most amply investigated chemical transformations, examples of

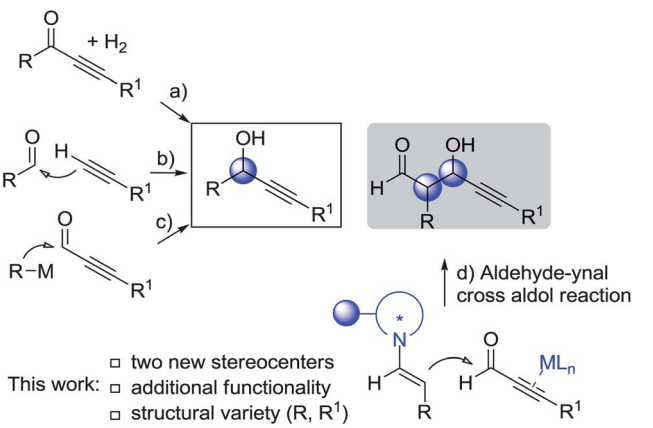

Fig. 1 Fundamental routes to propargylic alcohols and our strategy.

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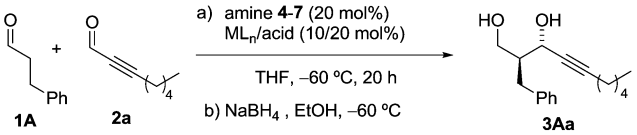
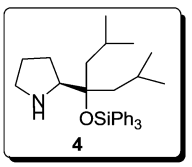
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided. See DOI: 10.1039/c3sc51027a

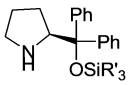
‡ These authors contributed equally to this work.

Table 1 Catalysts screening for the direct cross aldol reaction between **1A** and **2a**[a]

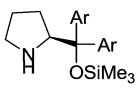


Entry	Amine	ML_n	Acid	Conv. (%)	Yield[b] (%)	*anti* : *syn*[c]	ee[d] (%)
1	**4**	—	—	NR	—	—	—
2	**4**	CuI	—	40	—	6 : 1	98
3	**4**	—	$PhCO_2H$	65	—	7 : 1	94
4	**4**	CuI	$PhCO_2H$	>95	71	>20 : 1	99
5	**4**	$Cu(OAc)_2$	$PhCO_2H$	>95	72	>20 : 1	99
6	**4**	Ph_3PAuCl	$PhCO_2H$	>95	73	19 : 1	97
7	**4**	$Rh_2(OAc)_4$	—	45	—	—	—
8	**4**	$Rh_2(OAc)_4$	$PhCO_2H$	>95	70	>20 : 1	97
9	**4**	AgOAc	$PhCO_2H$	>95	68	>20 : 1	99
10	**5**	$Cu(OAc)_2$	$PhCO_2H$	74	55	2 : 1	97
11	**6**	—	$PhCO_2H$	60	—	1.5 : 1	97
12	**6**	CuI	$PhCO_2H$	73	48	1.5 : 1	99
13	**7**	CuI	$PhCO_2H$	33	—	2.5 : 1	98





5 R': Me
6 R': Ph



7 Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (mol ratio of **1**/**2**/**3**/ML_n/acid, 3 : 1 : 0.2 : 0.1 : 0.2). [b] Isolated yield of cross aldol product after reduction to diol. [c] Determined by ^{1}H NMR, >20 : 1 means the minor diastereomer was not observed in the 300 MHz ^{1}H NMR. [d] ee of major diastereomer determined by chiral HPLC. NR: no reaction observed.

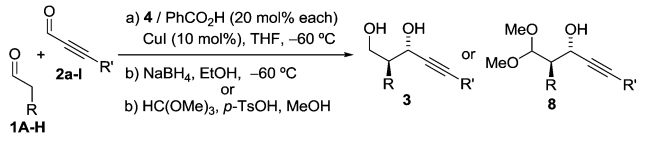
enantioselective aldol reactions involving α,β-ynals have been seldom reported in literature,[4] and the problem of reaction stereoselectivity for these types of substrates, particularly *syn*/*anti* diastereoselectivity,[5] has remained unsolved.[6] The only systematic study is that of Carreira *et al.*, who described the Ti-catalyzed acetate-aldol addition reaction of silyl ketene acetals with ynals.[7] The propargylic aldol adducts were obtained in high enantioselectivity, but no examples involving α-substituted enolate equivalents were reported. Whilst the specific reasons that make ynals particularly difficult aldehyde substrates for reaction stereocontrol remain intriguing, we speculated that their linear shape might constitute a detrimental structural feature. Indeed, the use of preformed ynal–hexacarbonylcobalt complexes, instead of naked ynals, has been shown to significantly increase the diastereoselectivity of aldol reactions with silyl enol ethers, apparently because of the increased bulk of the ynal–metal complex.[8]

Accordingly, we sought to establish a general and highly stereoselective direct aldol reaction of ynals based on a novel cooperative catalysis featuring the following reaction design elements: activation of donor carbonyl (aldehyde) *via* chiral enamine catalysis[9] and concomitant activation of acceptor carbonyl (ynal) *via in situ* and reversible ynal–metal complexation. While the realization of this idea faces considerable challenges, specifically the complications inherent in the aldehyde–aldehyde cross aldol reaction[10–12] and the problem of eventual catalysts inactivation *via* acid–base self-quenching,[13] if successful, a new entry for the stereoselective construction of functionalized propargylic alcohols would emerge.

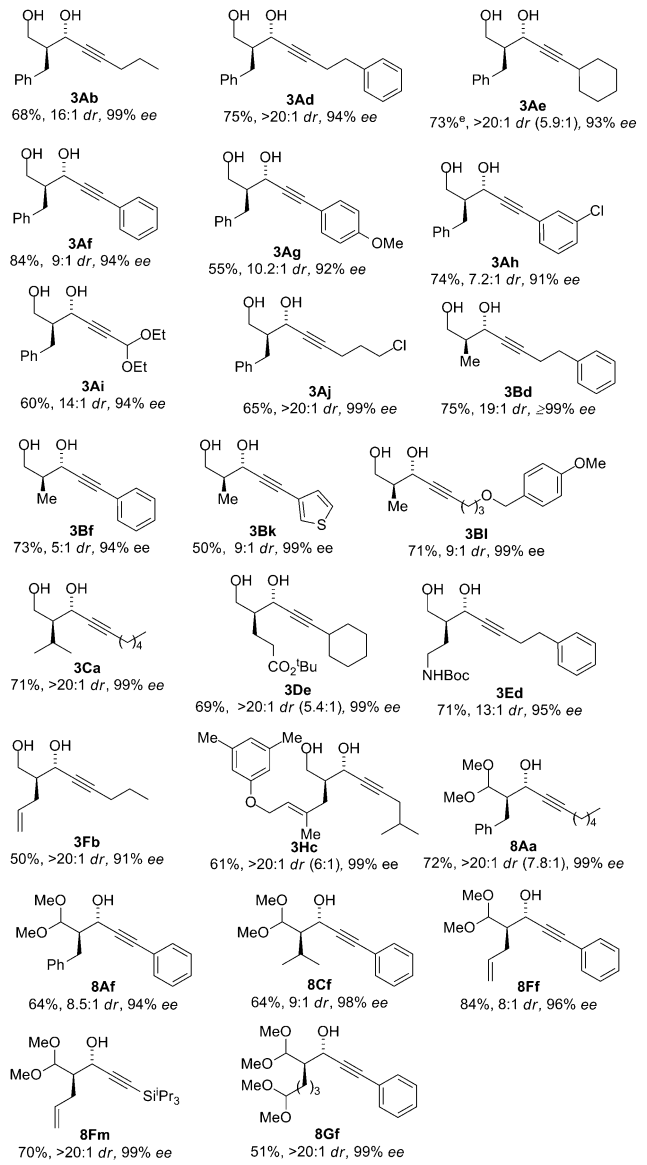
Catalysts screening and reaction optimization

To validate the above hypothesis, we set out to study the reaction of hydrocinnamaldehyde **1A** and propargyl aldehyde **2a** in the presence of prolinol ether **4**, an effective chiral catalyst previously developed by us for the enantioselective Mannich reactions of aldehydes with alkynyl imines.[14] Initial experiments carried out in parallel with **4** as the only catalyst (Table 1, entry 1) or with a combination of **4** and a carbophilic metal salt, such as CuI (entry 2), showed a promising cooperative effect. Thus while no reaction was observed at all with only **4**, in the presence of CuI cocatalyst around 40% reaction conversion was measured after 20 h at −60 °C. A similar cooperative effect was also observed when **4** was employed in combination with a Brønsted acid cocatalyst (entry 3).[15] In both cases diol **3Aa** was produced with a suboptimal *anti* : *syn* ratio, typically 7 : 1, albeit this selectivity is superior to that previously reported for direct aldol reactions involving ynals, *vide supra*. At this point our feeling was that while both the metal salt and the Brønsted acid seem to provoke similar catalytic effects, their modes of action might be distinct and therefore both cocatalysts may complement each other rather than cancel one another.

Table 2 Scope of the catalytic cross aldol reaction of ynals[a]



yield,[b] anti:syn ratio,[c] ee of anti isomer[d]

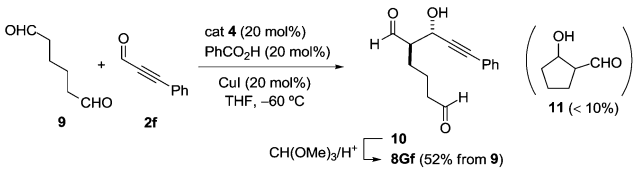


[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (mol ratio **1** : **2** : **3** : BA : CuI, 1.5–1.2 : 1 : 0.2 : 0.2 : 0.1). [b] Combined yield of the *anti* : *syn* cross aldol mixture after chromatography. [c] Determined by ^{1}H NMR and corroborated by HPLC; data in parentheses refer to reactions carried out with benzoic acid as the sole cocatalyst. [d] Determined by chiral HPLC. [e] No reaction observed using CuI as the sole cocatalyst.

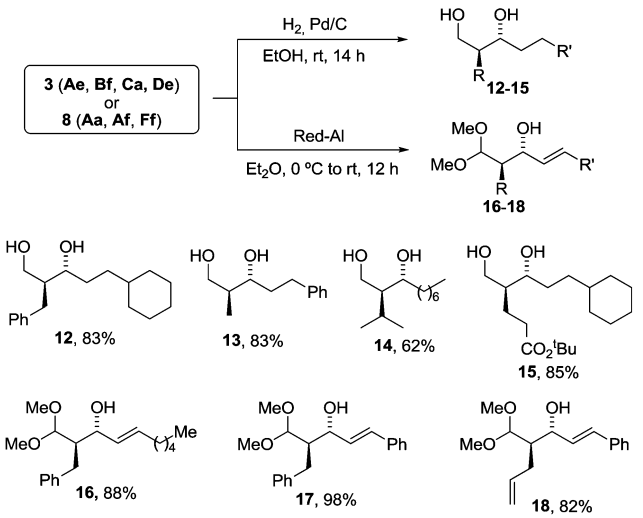
Indeed, to our delight, the reaction carried out in the presence of **4**, CuI or $Cu(OAc)_2$ (10 mol%), and benzoic acid (20 mol%) (entries 4 and 5) not only was complete after 16–20 hours at −60 °C, providing **3Aa** in about 70% isolated yield, but most remarkably, *anti*-isomer was formed almost exclusively and in 99% ee. Consequently, these results indicated that each catalyst component, namely amine, metal salt, and Brønsted acid is crucial for the optimum reaction outcome. We also observed that reaction temperature is critical to suppress aldehyde self-aldolization; at −40 °C or temperatures above, homodimerization occurred to varying extents regardless of the presence or absence of the metal cocatalyst. On the other hand, experiments carried out with metal cocatalysts other than copper, such as Au(I), Rh(II) or Ag(I) derivatives (entries 6, 8, 9), clearly revealed that this cooperative effect is a general attribute of other carbophilic metal salts. In each case the *anti* aldol was formed as essentially the sole isomer with very high enantioselectivity. As evidenced by these results, a distinguishing feature of the present synergistic transition metal–organocatalysis strategy with alkynyl substrates is that, contrary to most previous developments, no reaction at the carbon–carbon triple bond occurred.[16] To investigate the role played by the metal counterion in the ternary catalyst system, subsequent experiments were carried out using CuOTf and $Cu(OTf)_2$, respectively, in place of CuI and $Cu(OAc)_2$. Under these conditions, no reaction occurred, indicating that the Lewis acid character of the metal salt is important for reactivity. Further experiments eventually showed that while the **4**–$InCl_3$–$PhCO_2H$ catalyst system achieved some activity (30% conversion, *anti* : *syn* 2 : 1), other systems containing $Zn(OTf)_2$, $FeCl_3$, $AuCl_3$, or $YbCl_3$ as the metal cocatalyst were totally ineffective for this reaction. Finally, the importance of amine catalyst **4** was assessed by performing reactions under otherwise similar conditions but in the presence of the standard pyrrolidine catalysts **5**–**7**.[17] As the results in the table show, in these latter cases both reactivity and diastereoselectivity were eroded (entries 10–13), thus demonstrating that while possessing a closely related structure, the aryl to alkyl shift in the amine catalyst side chain may in certain situations be highly effective.[18]

Reaction scope and adducts application

With the optimized conditions in hand we explored the reaction scope using a representative selection of enolizable aldehydes and ynals. Adducts were isolated as the corresponding diols or acetals, respectively (Table 2). Not only ynals with hydrocarbon (phenyl, cyclic alkyl, and acyclic alkyl) pendant chain, but also those bearing a silyl, ether, acetal, chloro, or thiophene groups were all tolerated almost equally. Significantly, no *N*-alkylation of the amine catalyst using chloro-ynal **2j**, nor metal catalyst inactivation using thiophene ynal **2k**, was observed. With respect to the nature of the donor aldehyde component, short alkyl chain aldehydes such as propanal, longer chain aldehydes such as heptanal or hydrocinnamaldehyde, or even aldehydes bearing side chains with functional groups such as alkene, carbamate, ester, ether, and acetal, participated satisfactorily, giving high diastereoselectivities and generally excellent ee's. As the results in Table 2 show, ynals with alkyl substituents provided, with one exception (**3Bl**), the addition products in dr's greater than 13 : 1



Scheme 1 Chemoselective cross aldol reaction of dialdehyde **9**.



Scheme 2 Primary utility of propargylic adducts **3** or **8**.

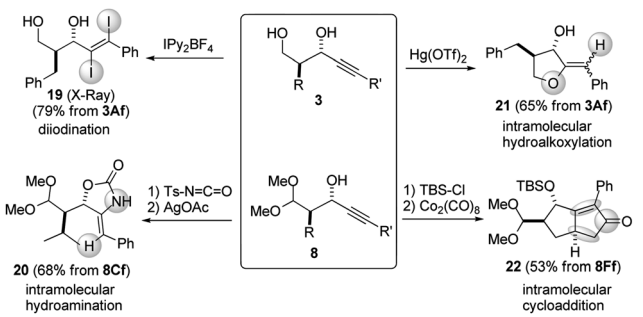


Fig. 2 Selected products synthesized from aldol adducts **3** or **8**.

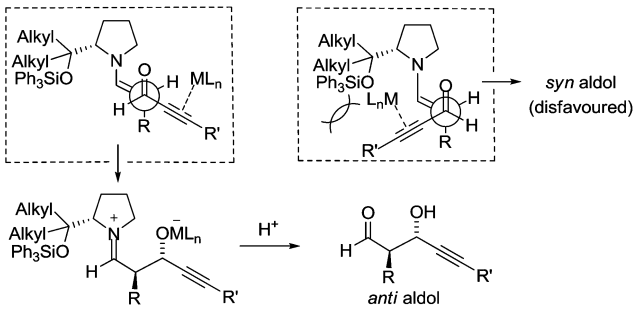


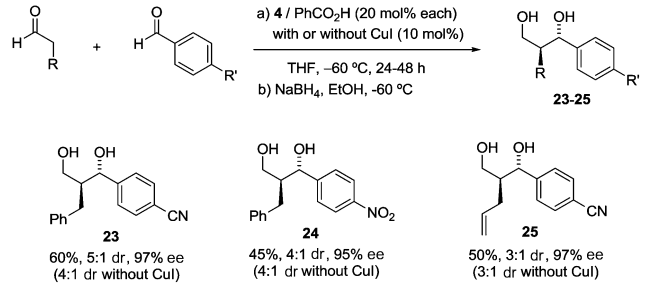
Fig. 3 Approaching geometries that might account for the observed preference of *anti* over *syn* aldol product formation.

and ee's in the range of 94–99%, whereas ynals with aryl substituents generally gave products with dr's from 7 : 1 to 10 : 1 and slightly lower ee's, typically 92–94%. On the other hand, experiments showed once again that the three components of the catalyst system, *i.e.* amine, metal salt and Brønsted acid, were necessary to achieve good levels of reactivity and stereoselectivity. Thus, for compounds **8Aa**, **3Ae**, **3De** and **3Hc**, in the absence of either benzoic acid or CuI cocatalyst, inferior (typically 6 : 1) *anti* : *syn* selectivity or lack of reactivity was observed. Of practical interest is also the fact that under optimized conditions (THF, −60 °C) neither a syringe pump technique to preclude aldehyde homodimerization,[10] nor a large excess of the donor aldehyde with respect to the acceptor (typical mol ratio 1.5–1.2 to 1, see Table 2) were necessary,[11] a relevant consideration when expensive aldehydes or aldehydes requiring multi-step synthesis are involved. It is worth noting that under the studied conditions, products from an eventual 1,4-addition were not formed to any significant extent. Thus, the present catalyst system allows straightforward exploitation of the ynal 1,2-reactivity pattern at the expense of the 1,4-addition pathway, which is generally exhibited by these aldehydes upon iminium activation catalysis.[19]

Interestingly, our reaction design is applicable to more complex scenarios where manifold inter- and intramolecular aldol pathways may compete. For instance (Scheme 1), treatment of **9** and phenylpropargyl aldehyde **2f** with catalyst **4**, benzoic acid and CuI in THF at −60 °C, furnished cross-aldol **10** as essentially a single isomer, which was isolated as acetal **8Gf** in 52% yield and 99% ee. Given the tendency of dialdehydes such as **9** to react intramolecularly leading to 5- and 6-membered carbocycles,[20] it is remarkable that under the above conditions the intramolecular aldol reaction product **11** was formed in only minute amounts (<10%).

The obtained aldol adducts are interesting building-blocks in their own right, but could also be easily transformed, as shown in Scheme 2, into their saturated analogs. For instance, catalytic hydrogenation of the triple bond in adducts **3Ae**, **3Bf**, **3Ca** and **3De** yielded the corresponding products **12–15**, which are products from a formal cross-aldol reaction between two dissimilar aliphatic aldehydes. Importantly, since the discovery of the amine-catalyzed direct intermolecular aldol reaction,[21] no direct aldol cross-coupling method is currently available for such a type of linear chain enolizable aldehydes.[22,23] Alternatively, controlled reduction of the triple bond in adducts **8** by treatment with Red-Al furnished **16–18** in high yields. The latter products are elusive and difficult to obtain through direct aldol reaction between aldehydes and the corresponding α,β-unsaturated aldehyde because of the prevalence of the enamine/iminium mediated 1,4-addition.[24]

Additional synthetic utility of the present catalytic cross-aldol methodology is illustrated in the transformation of the resulting propargylic adducts into a variety of structural motifs bearing two or more stereocenters, such as those depicted in Fig. 2.[25] This realization is of particular interest in that known methods for the enantioselective synthesis of propargylic alcohols, *vide supra*, may only generate a single stereocenter.[1c,2]



Scheme 3 Catalytic cross-aldol reaction with aromatic aldehydes.

Models for stereochemistry and catalysts action

Intrigued by the fact that α,β-ynals had not been employed before in enamine mediated aldol reactions, we carried out control experiments for the reaction between aldehyde **1A** and octynal (**2a**) in the presence of proline,[11a] α,α-diphenylprolinol,[11g,k] and α,α-bis(3,5-trifluoromethyl)phenylprolinol,[11g,k] three representative catalysts for aldol reactions. In all cases the corresponding aldol **3Aa** was obtained as a nearly equimolar mixture of *anti* and *syn* isomers,[25] a result that underlines once again the problem of controlling stereochemistry with α,β-ynals. The distinguishing capacity of our catalyst system to produce *anti*-configured aldol products would be consistent with an open transition state wherein the bulky substituent of the pyrrolidine ring of the enamine points away from the alkynyl group of the approaching aldehyde for minimal destabilization (Fig. 3). In this scenario, the Brønsted acid cocatalyst may play two roles: on the one hand, it may facilitate hydrolysis of the evolving metal aldolate and iminium groups, thus easing the recycling of the metal and amine catalysts; on the other hand, it may enhance the electrophilicity of the aldehyde group through hydrogen bonding. It may also perform both roles. If the above model is correct,[26] then the observed increase in *anti*-selectivity in the presence of a metal cocatalyst might be explained in terms of steric inflation of the alkyne moiety as a consequence of metal–alkyne association.[27]

Additional evidence in support of some kind of ynal-specific complexation to metals[28] was obtained from the aldol reactions involving aromatic instead of alkynyl aldehydes. In these instances (Scheme 3) the reaction outcome is essentially independent of the presence or absence of the metal cocatalyst.

Conclusions

In summary, we have reported the first direct organocatalytic aldol reaction of alkynyl aldehydes which enables a quick entry into stereoselective construction of functionalized propargylic alcohols. Through this method, adducts bearing two contiguous stereogenic centers in very high diastereo- and enantioselectivity (*anti*/*syn* up to >20 : 1 and ee up to >99%) are afforded, thus broadening the pool of currently available propargylic alcohols. Manipulation of adducts by trivial hydrogenation allows an easy, and perhaps the fastest known, route to some recalcitrant aldol assemblies such as those derived from two dissimilar enolizable aldehydes.[23] Key for that realization is the development of a ternary catalyst system comprised of a chiral pyrrolidine, a carbophilic transition metal salt, and a Brønsted acid, wherein each component is crucial for both chemical and stereochemical efficiency. The study uncovers a new case of chiral enamine catalysis in which α,α-dialkylprolinol ethers perform better than their parent α,α-diaryl analogs.[18] Given their ready and easy accessibility, this subclass of amine catalysts may therefore be a good help for new developments. The present work also demonstrates that the previously known metal–ynal complexation strategy for aldol reaction stereocontrol may be made catalytic in metal. We believe that this latter finding might have further applications in other (organo)catalytic transformations involving alkynyl substrates and work in that direction is currently ongoing in our laboratory.

Acknowledgements

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5 Representative literature data: ref. 4*a* (3 examples) 77%–88% ee, no *syn*/*anti* products; ref. 4*b* (1 example) *syn*/*anti* 75 : 25, ee's 78% (*syn*), 81% (*anti*); ref. 4*c* (3 examples) *syn*/*anti* from 52 : 48 to 67 : 33, racemic; ref. 4*d* (2 examples) *syn*/*anti* 52 : 48 and 51 : 49, racemic; ref. 4*e* (1 example), 61% ee, no *syn*/*anti* products; ref. 4*f* (1 example), *syn*/*anti* 2.2 : 1, 92% ee (*syn*); ref. 4*g* (6 examples), *syn*/*anti* essentially 1 : 1, racemic; ref. 4*h* (4 examples, ynones), *syn*/*anti* essentially 1 : 1, racemic.

6 As a remarkable exception, Denmark has reported the phosphoramidite-catalyzed aldol reaction of a preformed enol trichlorosilane with phenylpropargyl aldehyde as the only ynal to proceed in extremely high (98 : 2) *syn*/*anti* selectivity, although moderate (76% ee at best) enantioselectivity: S. E. Denmark and S. K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 4759–4762.

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