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Deciphering substitution effects on reductive hydroalkoxylation of alkynyl aminols for stereoselective synthesis of morpholines and 1,4-oxazepanes: total synthesis of tridemorph and fenpropimorph†‡

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Acid catalysed reductive etherification of *N*-propargyl amino alcohols for the stereoselective synthesis of *cis*-2,5/2,6-disubstituted morpholines and *cis*-2,6/2,7-disubstituted oxazepanes has been developed. Mechanistic studies revealed that terminal alkynols gave morpholines *via* a 6-*exo-dig* hydroalkoxylation–isomerization–reduction cascade. Interestingly, an alkyne hydration–cyclization–reduction sequence is found to be involved in the formation of oxazepanes from alkyl substituted internal alkynols. The strategy was used as a key step in the total synthesis of fungicides tridemorph and fenpropimorph.

1,4-Heterocycles have attracted considerable attention because of their ubiquity in natural products and bioactive molecules. Among them, substituted morpholines are not only present in agrochemicals but also can act as property-enhancing functional groups in drug discovery.[1] This is due to the well-balanced lipophilic–hydrophilic profile, relatively weak basicity, and chair-like flexible conformation of morpholines. For example, tridemorph (**1**) and fenpropimorph (**2**), introduced by BASF, Germany, act as cereal fungicides, especially for the control of powdery mildews (Fig. 1).[2] Sch 50911 (**3**) is a selective GABA B antagonist, which works as an anticonvulsant.[3] Similarly, the 1,4-oxazepane unit is found in naturally occurring alkaloids, such as dopamine D4 receptor ligand **4** used for the treatment of neurological disorders and oxazepane **5**, a peripheral-selective noradrenaline reuptake inhibitor.[4] Besides this, they also have a wide range of applications in enantioselective synthesis as chiral organocatalysts, chiral auxiliaries, and chiral templates in the synthesis of α-hydroxy acids and oxa-cycles. Not surprisingly, various methodologies have been developed for the synthesis of morpholine and oxazepane derivatives.

However, there are very few reports on the synthesis of 1,4-heterocycle derivatives using alkynes. In this context, the Huang group demonstrated gold(I)-catalyzed 6-*exo-dig* cyclization to afford morpholine and piperazine derivatives (Scheme 1, eqn (1)).[5] Recently, Panda *et al.* reported the synthesis of 3,4-dihydro-2*H*-1,4 oxazines *via* Ag(I) promoted intramolecular cyclization.[6] During the exploration of platinum catalysed domino cycloisomerization–hydroalkoxylation reactions of alkyne-diol derivatives for the synthesis of fused bicyclic acetals, the Ley group highlighted the potential regioselectivity problems in such transformations (Scheme 1, eqn (2)).[7] Similar potential regioselectivity issues were observed independently by Van der Eycken (for morpholine *vs.* oxazepine) and Schreiber (for oxazepanone *vs.* oxazocenones).[8] Despite the importance of these 1,4-heterocycles, common strategies which can give access to both morpholines as well as oxazepanes in a highly diastereoselective manner are uncommon. In this context, we have developed a Lewis acid mediated, highly

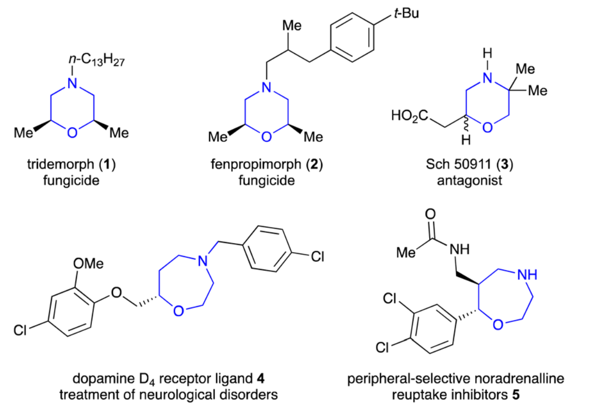

Fig. 1 Bioactive molecules having morpholine and 1,4-oxazepane cores.

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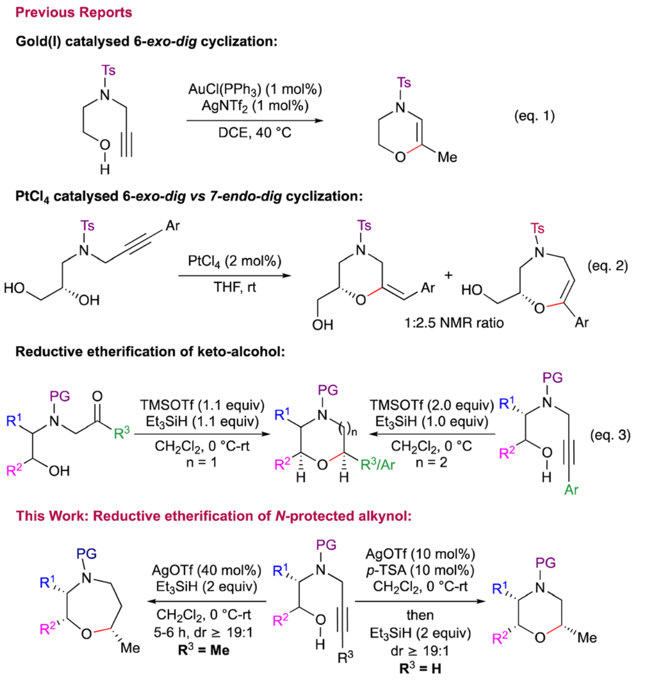
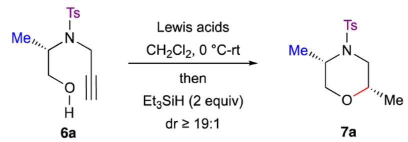
† Dedicated with profound respect to Prof. Sukh Dev on his 100th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization. CCDC 2356421 and 2356420. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ob00855c



Scheme 1 Synthesis of morpholines using alkynes.

Table 1 Optimization for the synthesis of morpholines



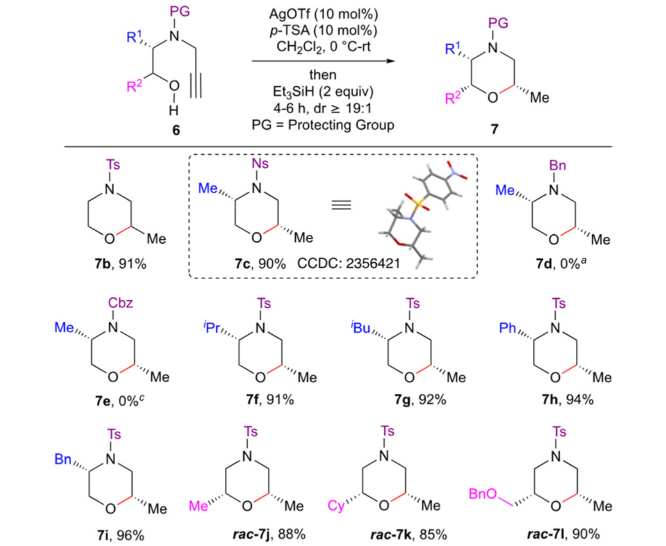
Entry	Acids[a]	Equiv.	Additive (equiv.)	Solvent	Time (h)	Yield[b] (%) (4a)
1	TMSOTf	4.0	—	CH_2Cl_2	72	—[c]
2	$Cu(OTf)_2$	1.0	—	CH_2Cl_2	72	—[c]
3	Ag(OTf)	0.4	—	CH_2Cl_2	4	94
4	Ag(OTf)	0.1	*p*-TSA (0.1)	CH_2Cl_2	4	95[d]
5	Ag(OTf)	0.05	*p*-TSA (0.1)	CH_2Cl_2	48	52
6	Ag(OTf)	0.1	*p*-TSA (0.1)	$(CH_2Cl)_2$	6	87
7	Ag(OTf)	0.1	*p*-TSA (0.1)	Toluene	24	40
8	Ag(OTf)	0.1	*p*-TSA (0.1)	CH_3CN	72	70
9	—	—	*p*-TSA (1.0)	CH_2Cl_2	72	0[e]
10	Ag(OTf)	0.1	MsOH (0.1)	CH_2Cl_2	24	30
11	$In(OTf)_3$	0.1	—	CH_2Cl_2	72	Trace
12	$Bi(OTf)_3$	0.1	—	CH_2Cl_2	48	23
13	$Sc(OTf)_3$	0.1	*p*-TSA (0.1)	CH_2Cl_2	24	22

[a] All reactions were carried out using alkynol **1** (0.20 mmol), with addition of acid at 0 °C–rt in dry solvent (3 ml). [b] Yield of isolated product after purification by silica gel column chromatography. [c] Starting material recovered. [d] Gram scale yield of **7a** 83%. [e] No reaction was observed even at reflux, only SM was recovered.

diastereoselective synthesis of morpholines as well as oxazepanes *via* reductive etherification of keto alcohols.[9] Further, TMSOTf mediated reductive etherification of aryl substituted *N*-alkynyl amino alcohols was shown to furnish oxazepanes, albeit with moderate to poor diastereoselectivity (Scheme 1, eqn (3)).[10] The reaction was found to be extremely sluggish with alkyl substituted alkynes under the conditions employed. In continuation of our program directed towards synthesis of oxa- and aza-cycles, herein, we disclose the reductive etherification of *N*-protected alkynols for the stereoselective synthesis of *cis*-2,5/2,6-disubstituted morpholines and *cis*-2,6/2,7-disubstituted oxazepanes. We also utilise the developed method for the total synthesis of fungicides tridemorph (**1**) and fenpropimorph (**2**).

Our study commenced with the reaction of *N*-protected alkynyl amino alcohol **6a** in the presence of TMSOTf (4.0 equiv.) and Et_3SiH (2.0 equiv.) in CH_2Cl_2 at 0 °C–rt, but no formation of the product **7a** was observed (Table 1, entry 1). Next, *N*-protected alkynyl amino alcohol **6a** was subjected to reductive etherification in the presence of $Cu(OTf)_2$ (1.0 equiv.) and Et_3SiH (2.0 equiv.) in CH_2Cl_2 at 0 °C–rt, and the reaction failed to give morpholine **7a** (Table 1, entry 2). When alkynol **6a** was treated with Ag(OTf) (0.4 equiv.) and Et_3SiH (2.0 equiv.), the reaction successfully furnished morpholine **7a** in excellent yield and diastereoselectivity (dr ≥ 19 : 1) (Table 1, entry 3). To reduce the loading of the Lewis acid, when *p*-TSA (0.1 equiv.) was used as an additive with Ag(OTf) (0.1 equiv.), the reaction indeed yielded the morpholine **7a** in excellent yield and diastereoselectivity (Table 1, entry 4). Further lowering the equivalents of Ag(OTf) resulted in a decreased yield of the product **7a** (Table 1, entry 5). Changing the solvent from dichloromethane to 1,2-dichloroethane, toluene or acetonitrile led to reduced yields (Table 1, entries 6–8). The reaction failed to furnish morpholine **7a** when *p*-TSA (1.0 equiv.) alone was used as the catalyst (Table 1, entry 9). Changing the additive to MsOH (0.1 equiv.) failed to improve the yield of morpholine **7a** (Table 1, entry 10). Other Lewis acids, such as $In(OTf)_3$, $Bi(OTf)_3$ and $Sc(OTf)_3$ gave the desired product **7a** (Table 1, entries 11–13) albeit in poor yield.

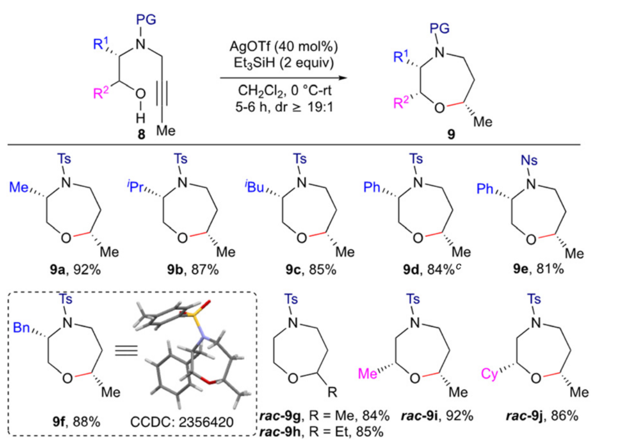
With the optimal conditions in hand, we next explored the scope of the reaction (Scheme 2). To begin with, the effect of the *N*-protecting groups on the efficiency of the reductive etherification was investigated. Thus, various protecting group containing alkynols **6b–e** were subjected to the optimised conditions. *N*-Sulfonylated alkynols **6b** and **c** worked well to furnish morpholines **7b** and **c** under these optimised conditions. On the other hand, L-alanine derived Bn and Cbz protected alkynols **6d** and **e** failed to give the desired products **7d** and **e**, even after increasing the catalyst loading (1 equiv. of both Ag(OTf) and *p*-TSA). Next, Lewis acid driven reductive etherification was employed for the enantiospecific synthesis of morpholine derivatives. L-Leucine, L-valine, L-phenylalanine and L-phenyl glycine derived alkynyl amino alcohols **6f–i** upon treatment with Ag(OTf)/*p*-TSA/Et_3SiH also gave the morpholine derivatives **7f–i** in an enantiospecific manner in good to excellent yield with excellent diastereoselectivity. Racemic alkynyl amino alcohols **6j–l** containing substituents Me, Cy and CH_2OBn *α* to the oxygen, afforded the corresponding morpholines **7j–l** in good yield. The reaction is amenable to 'gram scale' synthesis as demonstrated for the product **7a**. The structure and stereochemistry of the products **7** were assigned based on spectral data, including NOE, and was also unam-



Scheme 2 Stereoselective synthesis of highly substituted morpholines. Compounds **7c–i** are synthesized in an enantiospecific manner. Isolated yields. dr was measured by ^{1}H NMR on the crude reaction mixture. [a]Starting material recovered.

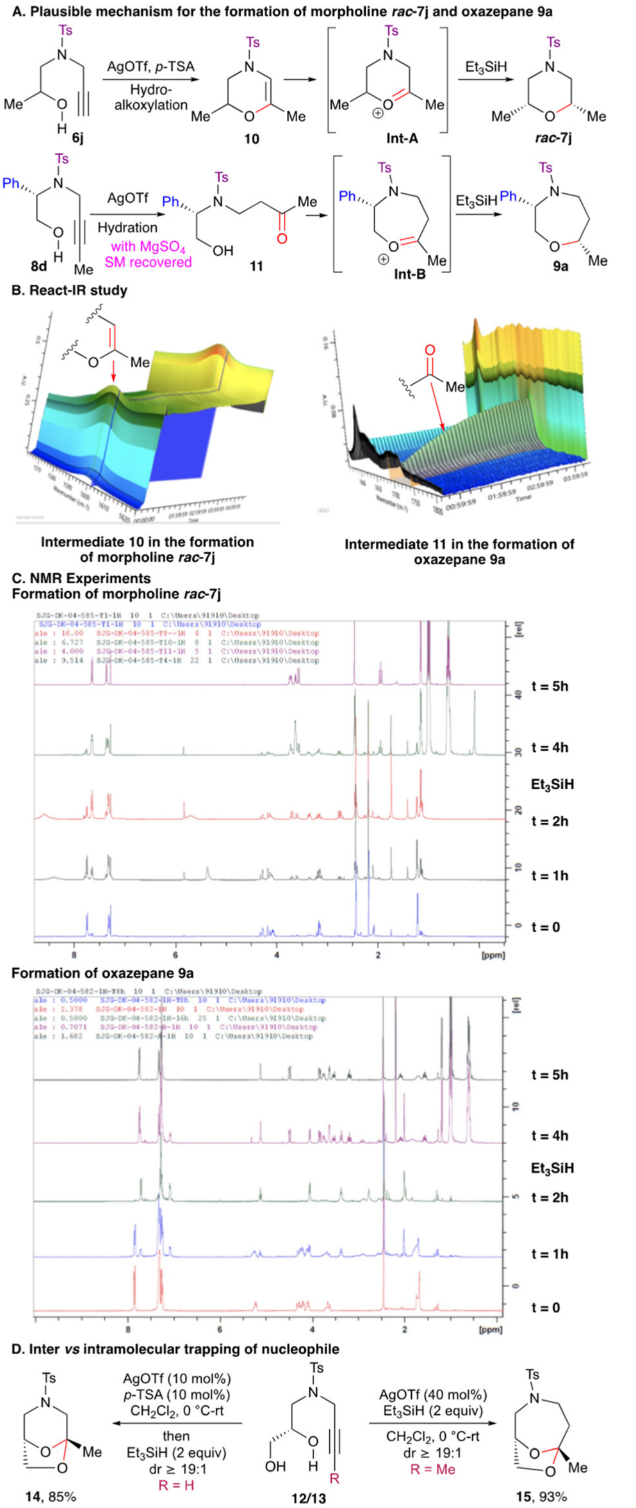
biguously confirmed by single crystal X-ray diffraction studies on morpholine **7c**.[11]

The significance of the methodology was further demonstrated by the synthesis of 1,4-oxazepanes (Scheme 3) by employing alkyl substituted internal alkynols **8** as the starting substrates. The enantiopure L-alanine, L-leucine, L-valine, L-phenylalanine and L-phenyl glycine derived alkynyl amino alcohols **8a–d** and **8f** were reacted with Et_3SiH (2.0 equiv.) in the presence of Ag(OTf) under the optimized reaction conditions, leading to the formation of 1,4-oxazepanes **9a–d** and **9f** in good yield and diastereoselectivity (dr ≥ 19 : 1). In the case of Ns protected alkynol **8e**, formation of 1,4-oxazepane **9e** was observed in good yield. Racemic substrates having substituents like Me and Cy, α to the oxygen, gave the corresponding 1,4-oxazepanes **9i** and **j** in good yield. The structure and stereochemistry of the product **9** were assigned based on spectral data, including NOE, and was also unambiguously confirmed by single crystal X-ray diffraction studies on the oxazepane derivative **9f**.[11]



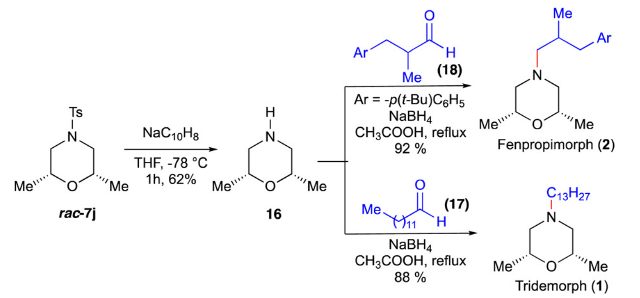
Scheme 3 Stereoselective synthesis of substituted 1,4-oxazepanes. Compounds **9a–f** are synthesized in an enantiospecific manner. Isolated yields. dr was measured by ^{1}H NMR on the crude reaction mixture. [a]Gram scale yield of **9d** 79%.

Mechanistically, the formation of the morpholines **7** and 1,2-oxazepanes **9** can be explained as follows (Scheme 4). *N*-Protected terminal alkynyl amino alcohol **6j** on treatment with Ag(OTf) underwent 6-*exo-dig* cyclization followed by isomerisation to generate intermediate **10**. Intermediate **10** on protonation generated oxonium ion **Int-A**, which on reduction with silane gave morpholine ***rac*-7j** (Scheme 4A). To prove the intermediacy of the 3,4-dihydro-oxazine **10**, the reaction course starting from *N*-protected terminal alkynyl amino alcohol **6j** to the morpholine ***rac*-7j** was monitored by react-IR. After the initiation of the reaction, the appearance of the absorption band at 1600 cm^{-1} corresponding to O–C═C stretching vibration denotes the formation of 3,4-dihydro-oxazine **10** (Scheme 4B). To corroborate this observation, the reaction was monitored by ^{1}H NMR spectroscopy as well. Treatment of terminal alkynyl amino alcohol **6j** with Ag(OTf)/*p*-TSA resulted in the disappearance of the singlet at 2.16 ppm and the appearance of a singlet at 5.81 ppm corresponding to C*H*═C(O)Me for 3,4-dihydro-oxazine **10**. Addition of Et_3SiH further led to the disappearance of the singlet at 5.81 ppm and appearance of a multiplet at 3.71–3.63 ppm for morpholine ***rac*-7j** (Scheme 4C). On the other hand, hydration of alkyl substituted alkynyl amino alcohol **8d** in the presence of Ag(OTf) furnished keto-alcohol **11**. Keto alcohol **11** reacted further to generate oxonium ion intermediate **Int-B**, which on reduction with silane yielded 1,2-oxazepane **9a** (Scheme 4A). The reaction course starting from internal alkynyl amino alcohol **8d** to the 1,2-oxazepane **9a** was monitored by react-IR. After the initiation of the reaction, the appearance of the absorption band at 1715 cm^{-1} corresponding to C═O stretching vibration gives credence to the formation of keto-alcohol **11** (Scheme 4B). Along with this, when an NMR study of the reductive etherification of internal alkynyl amino alcohol **8a** was carried out, in the presence of Ag(OTf)/Et_3SiH, disappearance of the triplet at 1.75 ppm and appearance of a singlet at 1.97 ppm denoted the formation of keto-alcohol **11.** Moreover, disappearance of the singlet at 1.97 ppm and appearance of a multiplet at 3.77–3.73 ppm signified the generation of 1,2-oxazepane **9a** (Scheme 4C). The stereochemical outcome of these reactions can be rationalised based on the model proposed in our earlier study. The substituent on the cyclic oxonium ion intermediate **Int-A/Int-B** occupies a pseudo-equatorial orientation to reduce steric interaction and delivery of the incoming hydride nucleophile from the axial direction results in a chair conformation for the 1,4-heterocyclic products.[9] Encouraged by this result, to further probe the regioselectivity, we decided to explore the reactivity of *N*-alkynylated diols. When terminal *N*-alkynylated diol **12** was subjected to reductive etherification, instead of the formation of the morpholine, spiro-ketal **14** was obtained. On the other hand, reaction of internal *N*-alkynylated diol **13** under the optimised conditions gave spiro-ketal **15** in place of the oxazepane



^{a}Isolated yield.

Scheme 4 Mechanistic investigation for the stereoselective synthesis of substituted morpholine and 1,4-oxazepanes. Isolated yields.



^{a}Isolated yield.

Scheme 5 Total synthesis of fungicides, tridemorph and fenpropimorph. Isolated yields.

(Scheme 4D). In both the cases, the intermediate oxonium ion was trapped by the internal hydroxy group as a nucleophile, rather than the silane. This is in contrast to our earlier studies where we obtained reductive etherification products while using TMSOTf as the catalyst.[9,10] The acetal opening followed by reduction in the present cases is perhaps precluded due to the mild Lewis acidic nature of Ag(OTf). These outcomes suggest that the terminal alkyne follows 6-*exo*-*dig* hydroalkoxylation whereas the internal alkyne follows a 7-*endo*-*dig* path exclusively.

After successfully demonstrating the scope of the strategy, we turned our attention to applying this strategy for the total synthesis of tridemorph (**1**) and fenpropimorph (**2**) (Scheme 5). The tosyl group of the morpholine ***rac*-7j** (*cf.* Scheme 2) was deprotected using sodium naphthalide to give the product **16** in good yield. Further imine formation with aldehydes **17** and **18** and reduction by $NaBH_4$ in the same pot furnished tridemorph (**1**) and fenpropimorph (**2**), respectively.

Conclusions

In conclusion, we have developed a reductive etherification-based strategy for the synthesis of diversely substituted morpholines and 1,4-oxazepanes in a highly diastereoselective manner. *cis*-2,5/2,6-Morpholines and *cis*-2,6/2,7-1,4-oxazepanes derived from enantiopure amino alcohols were prepared with good yields and excellent diastereoselectivities by utilizing this strategy. The developed strategy was also successfully applied in the stereoselective total synthesis of fungicides, tridemorph and fenpropimorph.

Conflicts of interest

There are no conflicts to declare.

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11 CCDC 2356421 **7(c)** and 2356420 **9(f)** contain the supplementary crystallographic data for this paper.†