Asymmetric Catalysis

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Organocatalytic Enantioselective Conia-Ene-Type Carbocyclization of Ynamide Cyclohexanones: Regiodivergent Synthesis of Morphans and Normorphans

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Abstract: *Described herein is an organocatalytic enantioselective desymmetrizing cycloisomerization of arylsulfonyl-protected ynamide cyclohexanones, representing the first metal-free asymmetric Conia-ene-type carbocyclization. This method allows the highly efficient and atom-economical construction of a range of valuable morphans with wide substrate scope and excellent enantioselectivity (up to 97% ee). In addition, such a cycloisomerization of alkylsulfonyl-protected ynamide cyclohexanones can lead to the divergent synthesis of normorphans as the main products with high enantioselectivity (up to 90% ee). Moreover, theoretical calculations are employed to elucidate the origins of regioselectivity and enantioselectivity.*

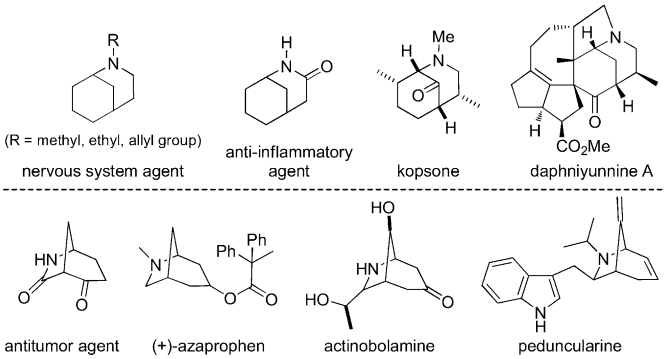

Figure 1. Morphans and normorphans in bioactive molecules and natural products.

Introduction

Structurally diverse and interesting family of bridged N-heterocycles, such as morphans and normorphans, are important structural motifs that have been found in a number of bioactive molecules and natural products (Figure 1).[1,2] Although many impressive strategies have been established for their construction in the past decades,[3,4] the practical synthesis of these medicinally significant structures remains an intriguing objective for the synthetic community, especially those with high enantioselectivity. To date, successful examples of asymmetric assembly of morphans and normorphans have been quite scarce,[3d,4c] and these methods often suffer from limited substrate scope, inaccessible starting materials, and low efficiency.

Recently, catalytic carbocyclization of alkynyl carbonyls or alkynyl silyl enol ethers has attracted considerable interest in organic synthesis because of its high bond-forming efficiency and atom economy in the formation of functionalized cyclic compounds.[5–8] Despite these significant achievements, examples of such an asymmetric version are quite scarce.[9–11] In 2005, Toste et al. reported the first enantioselective intramolecular Conia-ene reaction of alkynyl β-dicarbonyl compounds by employing a Pd^{II}/Yb^{III} dual catalyst (Scheme 1a).[9a] On the basis of this work, the relevant Conia-ene-type carbocyclizations were nicely explored by the groups of Shibasaki[9b] and Shibata[9c] by using a similar bimetallic cooperative catalysis. In addition, the enantioselective metallo-organocatalyzed carbocyclization was realized by Michelet, Ratovelomanana-Vidal, and co-workers and Enders and co-workers (Scheme 1b).[10] Very recently, Dixon et al. demonstrated an elegant protocol for the chiral silver complex and chiral amine cocatalyzed desymmetrization of 4-propargylamino cyclohexanones that led to enantioenriched morphans (Scheme 1c).[11] Although notable successes have been achieved, these asymmetric carbocyclization reactions have so far been limited to transition-metal catalysts, especially chiral metal complexes, and a metal-free protocol has not been reported to date.

Ynamides are special alkynes bearing an electron-withdrawing group on the nitrogen atom, and have proven to be versatile building blocks in organic synthesis over the past decade.[12] Importantly, the nitrogen atom is able to impose an

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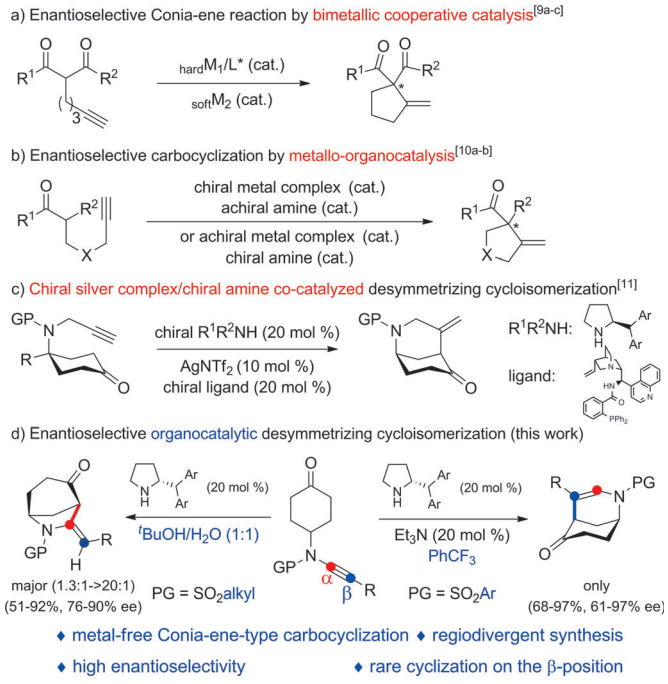


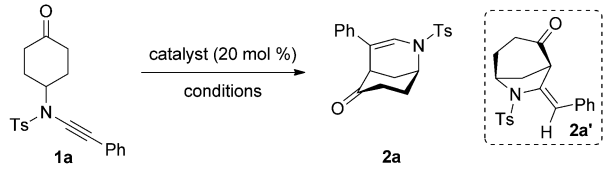
Scheme 1. Asymmetric catalytic carbocyclization of alkynyl carbonyls.

electronic bias, almost invariably rendering regioselective nucleophilic α-addition by a diverse range of nucleophiles via keteniminium intermediates under transition-metal and Brønsted acid catalysis. As a continuation of our work on developing ynamide chemistry for heterocycle synthesis,[13] we herein report the realization of an organocatalytic enantioselective desymmetrizing cycloisomerization of arylsulfonyl-protected ynamide cyclohexanones, which represents the first example of a completely metal-free asymmetric Conia-ene-type carbocyclization. In addition, a rare cyclization at the β-position of the ynamide is also achieved.[14] This protocol allows highly efficient and atom-economical construction of various valuable morphans with wide substrate scope and excellent enantioselectivity (Scheme 1 d). Moreover, a similar cycloisomerization of alkylsulfonyl-protected ynamide cyclohexanones can lead to the divergent synthesis of normorphans as the main products with high enantioselectivity. Theoretical calculations are employed to elucidate the origins of regioselectivity and enantioselectivity. Herein, we report the results of our detailed investigations of this organocatalytic enantioselective carbocyclization of ynamide cyclohexanones, including substrate scope, synthetic applications, biological tests, and mechanistic studies.

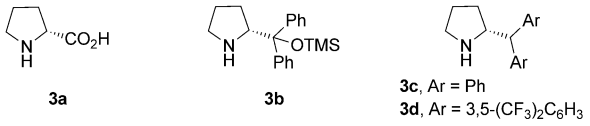
Results and Discussion

The cyclohexanone-tethered ynamide **1a** was chosen as the model substrate for our initial study, and selected results are listed in Table 1.[15,16] To our delight, the desymmetrizing cycloisomerization of **1a** proceeded smoothly in the presence of only proline (**3a**) as the catalyst, and importantly, the corresponding morphan **2a** was formed in 50% yield by an unusual addition at the β-position of the ynamide (entry 1).

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Reaction conditions	Yield [%][b]	*ee* [%][c]
1	**3a**	toluene (0.05 M), 80 °C, 72 h	50 (45)	<1
2	**3b**	toluene (0.05 M), 80 °C, 72 h	<1 (90)	<1
3	**3c**	toluene (0.05 M), 80 °C, 72 h	34 (60)	86
4[d]	**3c**	toluene (0.05 M), 80 °C, 48 h	85 (<1)	85
5[d]	**3d**	toluene (0.05 M), 80 °C, 72 h	10 (84)	96
6[e]	**3d**	toluene (0.05 M), 80 °C, 72 h	20 (71)	96
7[e]	**3d**	toluene (0.10 M), 80 °C, 72 h	35 (57)	95
8[e]	**3d**	toluene (0.20 M), 80 °C, 72 h	72 (19)	95
9[e]	**3d**	PhCl (0.20 M), 80 °C, 72 h	83 (8)	87
10[e]	**3d**	$PhCF_3$ (0.20 M), 80 °C, 36 h	95 (<1)	95
11[e,f]	**3d**	$^tBuOH/H_2O$ (1:1, 0.20 M), 80 °C, 64 h	41 (<1)	93



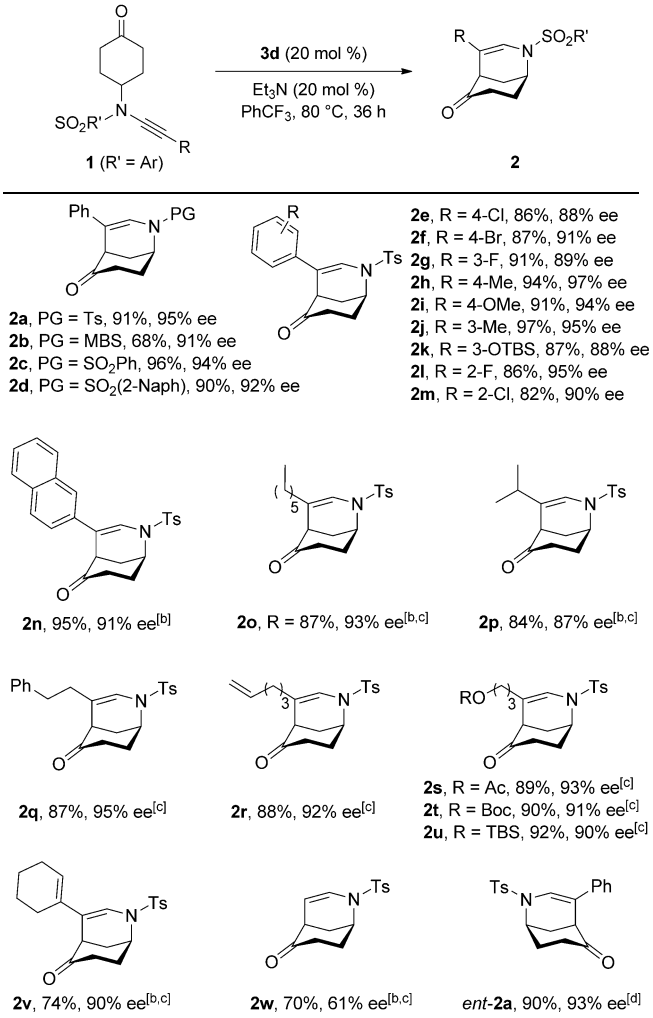
[a] Reaction conditions: **1a** (0.1 mmol), catalyst (20 mol%), solvent (0.05–0.20 M), 80 °C, 36–72 h in vials. [b] Measured by ^1H NMR spectroscopy using diethyl phthalate as an internal standard. Recovered unreacted starting material given within parentheses. [c] Determined by HPLC analysis. [d] 20 mol% of $^iPr_2EtN$ was used as additive. [e] 20 mol% of Et_3N was used as additive. [f] **2a'** was formed in 35% NMR yield. Ts = 4-toluenesulfonyl, TMS = trimethylsilyl.

Of note, previous silver-catalyzed carbocyclizations of enol-ether-tethered ynamides occurred exclusively at the α-position of the ynamide.[8a] Although the typically successful diarylprolinol silyl ether catalyst **3b** was inefficient in this reaction (entry 2), the sterically less demanding desilyloxy derivatives **3c–d** were found to be effective chiral organocatalysts (entries 3–6), and 96% *ee* was obtained in the presence of **3d** (entries 5 and 6). Interestingly, the use of tertiary amines as additives significantly accelerated the reaction efficiency (entries 3–6),[9f,17] whereas the use of only tertiary amine (without chiral secondary amine) gave no conversion at all, indicating no involvement of a racemic background reaction caused by the external base.[15] The tertiary amine here most likely serves as a base to promote the enamine formation via the reaction with **1a** for the generation of the enolate species and the protonated amine. Gratifyingly, subsequent investigations on the reaction concentration and solvent (entries 7–10) demonstrated that **2a** was obtained in 95% yield with 95% *ee* by using $PhCF_3$ (0.2 M) as the solvent (entry 10). It should be mentioned that the formation of the normorphan **2a'** was detected in 35% yield in the presence of $^tBuOH/H_2O$ (1:1) as the solvent (entry 11) while almost no **2a'** (<3%) was obtained in all of the other cases given above (entries 1–10).

With the optimal reaction conditions in hand (Table 1, entry 10), we then assessed the scope of this enantioselective

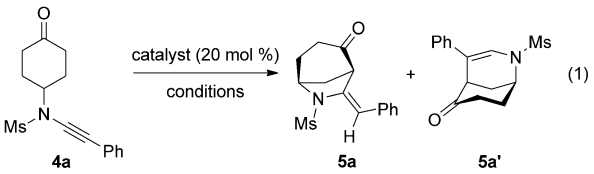
organocatalytic desymmetrizing reaction for the synthesis of morphans (**2**; Table 2). Besides the Ts-protected ynamide, the reaction also proceeded smoothly with MBS-, SO_2Ph-, and 2-Naph-protected ynamides, affording the desired morphans **2b** (68%, 91% *ee*), **2c** (96%, 94% *ee*), and **2d** (90%, 92% *ee*), respectively. In addition, various aryl-substituted ynamides bearing either electron-withdrawing or electron-donating groups were good substrates to afford products **2e–m** in 82–97% yields and 88–97% *ee*, and especially ynamides with *ortho*-substituted aryl motifs were also tolerated. The reaction was also extended to the naphthyl-substituted ynamide to produce the corresponding **2n** in 95% yield and 91% *ee*. Then, various alkyl-substituted ynamides were screened and the desired morphans **2o–u** were obtained in 84–92% yields and 87–95% *ee*. Notably, a range of functional groups were perfectly tolerated, including phenyl, alkenyl, and protected hydroxy. Moreover, this chemistry was also compatible with an alkenyl-substituted ynamide and even terminal ynamide to deliver the desired products **2v** and **2w** in good yields, albeit with a significantly reduced enantiocontrol in the latter case. Our attempts to extend the reaction to the cyclobutanone ynamide **1x**, acyclic ketone ynamide **1y**, and aldehyde ynamide **1z** have been unsuccessful,[18] and attempts to prepare the heterocycle-substituted ynamides failed.[15] Finally, the use of *ent*-**3d** as the chiral organocatalyst led to the efficient formation of the desired *ent*-**2a** (93% *ee*). Importantly, an unusual cyclization on the β-carbon atom of the ynamide was achieved in all these cases (attack on the α-carbon: < 3%). Thus, this protocol provides a highly efficient and practical route for the synthesis of valuable enantioenriched morphans.

Table 2: Reaction scope for the formation of chiral morphans **2**.[a]



[a] Reaction conditions: **1** (0.2 mmol), **3d** (0.04 mmol), Et_3N (0.04 mmol), $PhCF_3$ (1 mL), 80 °C, 36 h, in vials. Yields are those of isolated products. The *ee* values were determined by HPLC analysis. [b] Time = 64 h. [c] [**1**] = 0.40 M. [d] Used *ent*-**3d**. Ac = acetyl, Boc = *tert*-butoxycarbonyl, MBS = 4-methoxybenzenesulfonyl, Naph = naphthyl, PG = protecting group, TBS = *tert*-butyldimethylsilyl.

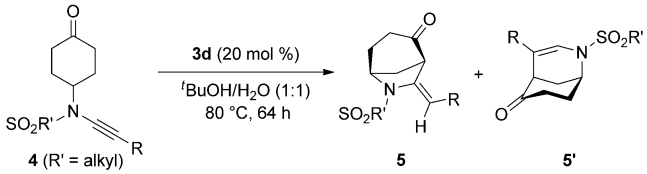
Interestingly, when the Ms-protected ynamide **4a** was employed under the above optimized reaction conditions, the corresponding normorphan **5a** was obtained as a major product with only the *E* configuration of the double bond [Eq. (1)],[19] which is distinctively different from the related silver-catalyzed protocol by Miesch and co-workers where a *Z*-configured *exo* double bond was formed through the favorable conformation of the keteneiminium intermediate.[8a] Further studies revealed that a higher ratio of **5a**/**5a′** was obtained in the presence of pyrrolidine as catalyst and ^{t}BuOH as solvent while chiral **5a** was formed in 58% yield (NMR) with 90% *ee* by employing **3d** as chiral catalyst under the optimized reaction conditions.[15]

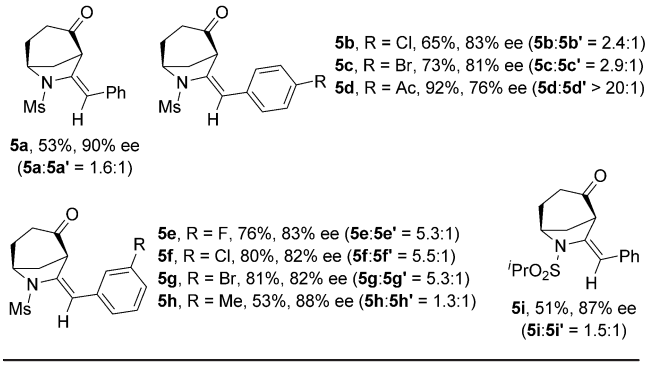


catalyst	conditions	yield of **5a**	**5a**:**5a'**	ee of **5a**
pyrrolidine	$PhCF_3$, 60 °C, 9 h	60%	1.5:1	/
pyrrolidine	^{t}BuOH, 60 °C, 4 h	75%	3.0:1	/
3d	^{t}BuOH/H_2O (1:1), 80 °C, 64 h	58%	1.6:1	90%

Inspired by these results, we also examined the scope of this enantioselective organocatalytic desymmetrizing reaction for the synthesis of the normorphans **5**. As depicted in Table 3, the reaction proceeded well with a variety of aryl-substituted ynamides (**4**), including the isopropylsulfonyl-protected ynamide **4i**, leading to the formation of functionalized normorphans (**5a–i**) in moderate to excellent yields with 76–90% *ee*. Instead, when the alkyl-substituted ynamide **4** (R = alkyl) was employed, the formation of the corresponding morphan **5′** was observed as the main product.[15] In addition, excellent *E*/*Z* ratios (> 50:1) of the newly generated olefin moieties were observed in all cases. Of note, all the regioisomers were readily isolated by column chromatography, and higher **5**/**5′** ratios could be obtained in case of aryl-substituted ynamides with electron-withdrawing groups. The absolute configuration of **5h** was established by X-ray diffraction analysis (Figure 2).[20]

Table 3: Reaction scope for the formation of the chiral normorphans **5**.[a]





[a] Reaction conditions: **4** (0.2 mmol), **3d** (0.04 mmol), ^{t}BuOH/H_2O (1/1; 1 mL), 80 °C, 64 h, in vials. Yields are those of isolated products. The *ee* values were determined by HPLC analysis. Ms = methanesulfonyl.

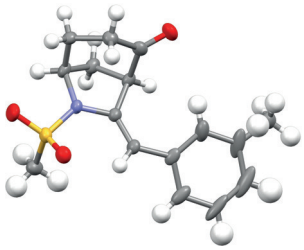
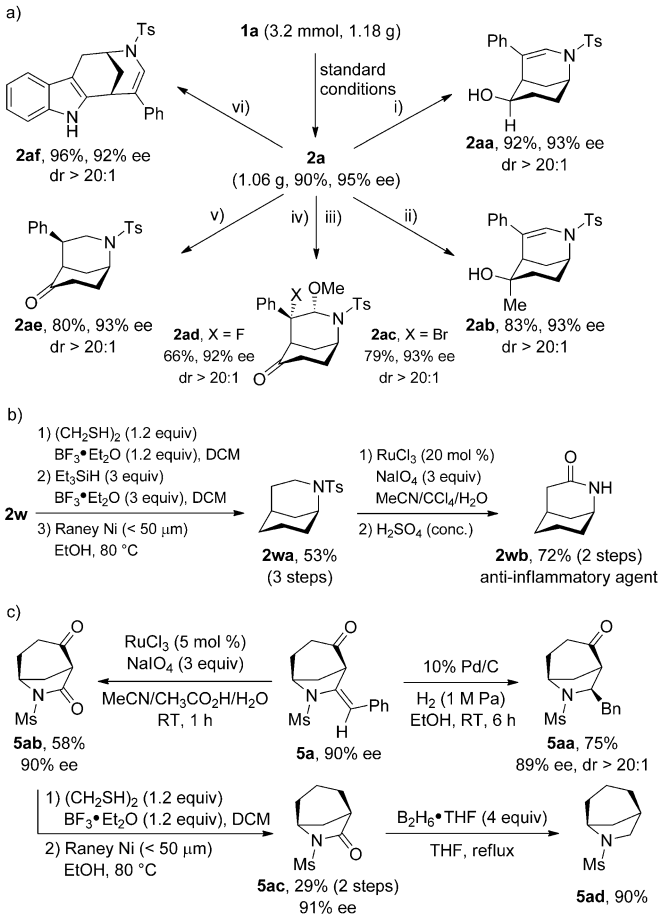


Figure 2. Structure of **5h** in its crystal.

Further synthetic transformations of the as-synthesized chiral morphans and normorphans were then explored (Scheme 2). For example, chiral **2a**, prepared on a gram scale in 90% yield with 95% *ee*, could be readily converted into the desired products **2aa** (92%, 93% *ee*) and **2ab** (83%, 93% *ee*), respectively, by treatment with $NaBH_4$ and MeMgBr. Interestingly, the use of NBS and Selectfluor led to the selective difunctionalization of the double bond from the less hindered face to produce the corresponding **2ac** and **2ad** with three contiguous stereocenters in good yields. In addition, facile hydrogenation of the double bond afforded the desired **2ae** in 80% yield with 93% *ee*. Moreover, the synthesis of the indole-fused morphan **2af** was achieved in 96% yield upon exposure to $PhNHNH_2$ and TsOH (Scheme 2a). The absolute configurations of **2ad** and **2ae** were confirmed by X-ray diffraction analysis (Figures 3 and 4),[20] which also determined the absolute configuration of the morphans **2**. The synthesis of the anti-inflammatory agent **2wb**[1c] was also achieved, starting from **2w**, through reduction of the alkenyl and carbonyl groups, followed by oxidation of the methylene group adjacent to the nitrogen center and removal of the Ts group (Scheme 2b). Finally, the reduction and oxidation of the double bond of **5a** afforded the corresponding **5aa** (75%,



Scheme 2. Gram-scale reaction and synthetic applications. Reagents and conditions: i) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 0.5 h; ii) MeMgBr (2 equiv), THF, 0 °C, 4 h; iii) NBS (2 equiv), DCM/MeOH (1:1), RT, 5 min; iv) Selectfluor (2 equiv), MeCN/MeOH (2:1), −40 °C, 11 h; v) 10% Pd/C, H_2 (2 M Pa), EtOAc, RT, 24 h; vi) $PhNHNH_2$ (2 equiv), TsOH (2 equiv), toluene, 80 °C, 6 h.

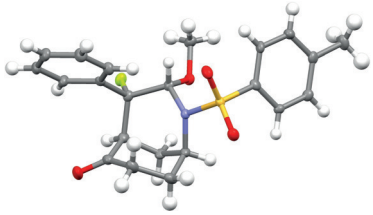


Figure 3. Structure of **2ad** in its crystal.

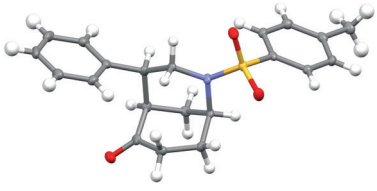


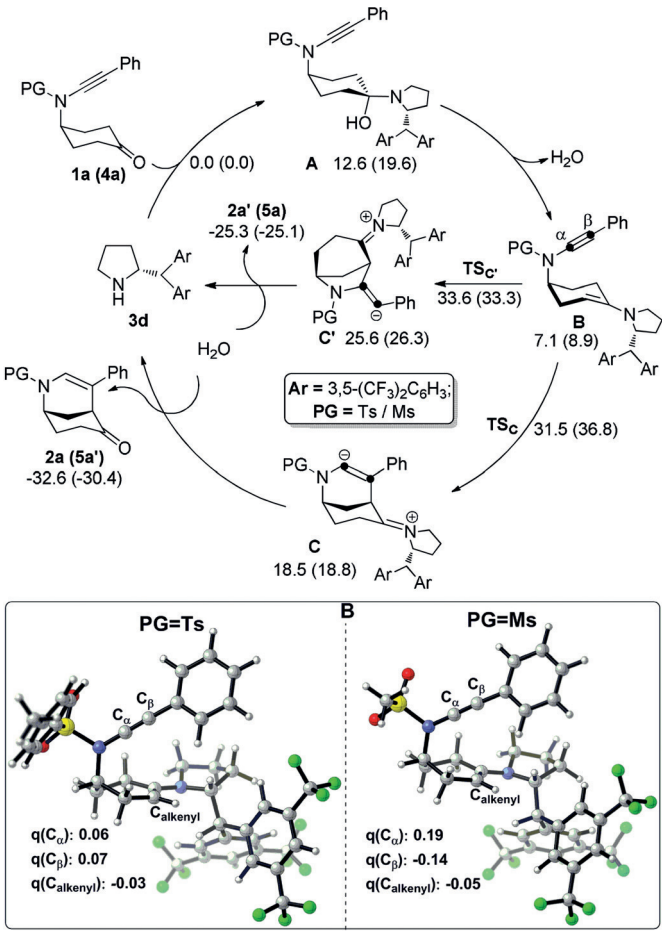
Figure 4. Structure of **2ae** in its crystal.

89% *ee*) and **5ab**[2a,21] (58%, 90% *ee*), respectively. The latter could be further transformed into the corresponding **5ac** (29%, 2 steps, 91% *ee*) and **5ad** (90%; Scheme 2c). Importantly, the enantioselectivities were well maintained and excellent diastereoselectivities (d.r. > 20:1) were achieved in all these transformations.

Moreover, we also tested the newly synthesized morphans and normorphans for their bioactivity as antitumor agents. The cytotoxic effects of these compounds were evaluated against a panel of cancer cells, including breast cancer cells MDA-MB-231 and MCF-7, melanoma cells A375, and esophageal cancer cells SK-GT-4 and KYSE-450, based on cell viability assays.[15] Our preliminary studies revealed that almost half of these morphans exhibited significant cytotoxic effects on MDA-MB-231 and A375, and a few morphans exhibited cytotoxic effects on SK-GT-4 and KYSE-450, whereas the normorphan derivatives displayed weak antitumor activity against these five cell lines.

On the basis of the previous results[8–11] and density-functional theory (DFT) computations,[15] plausible mechanisms for regiodivergent synthesis of morphans and normorphans are illustrated in Scheme 3. Initially, an amine–ketone condensation between pyrrolidine **3d** and the ynamide-tethered cyclohexanone via intermediate **A** gives the enamine intermediate **B**. The nucleophilic carbon site of its enamine group can attack either the β or α position of the ynamide group to form vinyl anion intermediates **C** or **C′**, respectively.[22] As Ts is more electron-withdrawing than Ms, the β and α carbon of the Ts-containing ynamide are both positively charged and the nucleophilic attack favors the β site to form a sterically less strained six-membered-ring intermediate **C** that leads eventually to **2a**. In the case of PG = Ms, the β carbon is negatively charged, and the nucleophilic addition thus favors the positively charged α carbon site to form a sterically more strained five-membered-ring intermediate **C′**, the precursor of **5a**. The observed protecting-group-dependent regiodivergence can be attributed to the stronger electron-withdrawing capability of Ts than Ms in the ynamide substrate. Furthermore, more detailed DFT computations showed that the regioselectivity of cyclization is much more sensitive on the polarity of solvent in the case of PG = Ts than in the case of PG = Ms.[15]

To understand the origin of enantioselectivity, the C–C bond-formation transition states (Figure 5) leading to the final product **2a** and its enantiomer were carefully explored. Among them, the transition-states $\mathbf{TS_C}$ and $\mathbf{TS_{C2}}$ having the bulky bis(aryl)methyl group and ynamide phenyl moiety located at the opposite side of the enamine plane are lower in free energy than $\mathbf{TS_{C1}}$ and $\mathbf{TS_{C3}}$, which have the bis-



Scheme 3. Plausible reaction mechanism. Relative free energies (Δ*G*, kcal mol^{-1}) of key intermediates and transition states were computed at the SMD-M06-2X/6-311 + G(d,p)//SMD-M06-2X/6-31G(d) level for reactions in solvent ($PhCF_3$ for the case of PG = Ts and $^tBuOH/H_2O$ (1:1) for the case of PG = Ms) at 298 K. Data for the case of PG = Ms are given within parentheses. The structures of key intermediates **B** as well as Mulliken charges (q) on selected atoms are also shown.

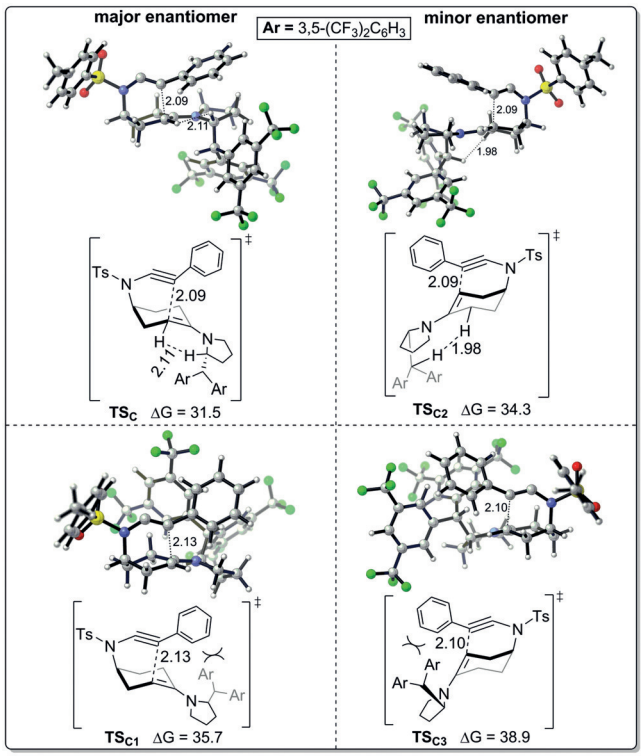


Figure 5. Optimized structures (key bond lengths in Å) and relative free energies (Δ*G*, kcal mol^{-1}) of the C–C bond formation transition states leading to **2a** and its enantiomer from **1a** catalyzed by **3d**.

(aryl)methyl group and ynamide phenyl moiety located at the same side of the enamine plane. More delicately, $\mathbf{TS_{C2}}$ has a shorter C–H···H–C distance than does $\mathbf{TS_C}$ (1.98 vs. 2.11 Å), hinting the former has a stronger C–H···H–C steric repulsion. As such, $\mathbf{TS_C}$ is the lowest in free energy, giving rise to a 2.8 kcal mol^{-1} ($\mathbf{TS_C}$ vs. $\mathbf{TS_{C2}}$) preference for the generation of major enantiomer. In short, the observed enantioselectivity is dominated by steric effects.

Conclusion

In summary, we have developed an organocatalytic enantioselective desymmetrizing cycloisomerization of arylsulfonyl-protected ynamide cyclohexanones, allowing the highly efficient and atom-economical construction of a range of valuable morphans with wide substrate scope and excellent enantioselectivity (up to 97% *ee*). To the best of our knowledge, this protocol not only represents the first metal-free asymmetric Conia-ene-type carbocyclization, but also constitutes the first ynamide reaction catalyzed only by an amine, which is transition metal and Brønsted acid free. In addition, a rare cyclization on the β-position of the ynamide is achieved. Moreover, such a cycloisomerization of alkylsulfonyl-protected ynamide cyclohexanones can lead to the divergent synthesis of various normorphans as the main products with high enantioselectivity (up to 90% *ee*). Further transformations and biological tests of these bridged N-heterocycles have been conducted, highlighting the potential utility of this chemistry. DFT studies were employed to elucidate the origins of regioselectivity and enantioselectivity, and it is revealed that both protecting group of the substrate and reaction solvent are the key factors governing regiocontrol. The present protocol offers new opportunities for the development of novel reactions of ynamides, especially those based on asymmetric catalysis.[23]

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · cyclizations · desymmetrization · heterocycles · organocatalysis

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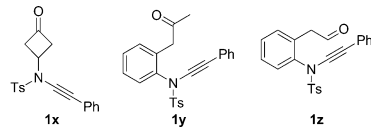

[19] We speculate that the *E* configuration of the double bond is attributed to thermodynamic factors as the alkenyl anion intermediate **C′** is presumably involved, as shown in Scheme 3.

[20] CCDC 1919345, 1919346 and 1919347 (**5h**, **2ad**, and **2ae**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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