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Brønsted Base-Catalyzed Tandem Isomerization–Michael Reactions of Alkynes: Synthesis of Oxacycles and Azacycles

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Abstract: An efficient synthesis of oxacycles and azacycles was developed using a Brønsted base-catalyzed tandem alkyne isomerization–Michael reaction sequence. Functionalized 2-alkylidenetetrahydrofurans were prepared by an intramolecular oxy-Michael reaction on an allene that was generated *in situ* from an alkynoate. The aza-Michael version using alkynylamines, alkynylamides and alkynyl carbamates led to piperidines, lactams and oxazolidinones, respectively. An enantioselective version of this reaction resulted in an axially chiral lactam with high enantioselectivity. Some alkynes, however, were unable to complete the intramolecular Michael reactions and provided enantioenriched allenes.

Keywords: 2-alkylidenetetrahydrofurans; azacycles; Brønsted bases; oxacycles; tandem isomerization–Michael reaction

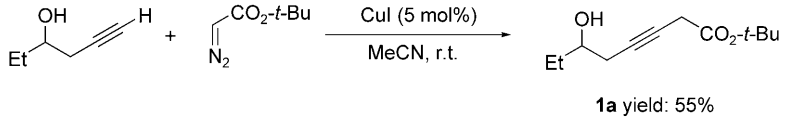
Introduction

Oxacycles and azacycles are important heterocyclic systems which are commonly found in natural products and valuable fine chemicals.[1] In particular, functionalized tetrahydropyrans and tetrahydrofurans are present in a variety of pharmacologically active natural products;[2] for example, the acetogenins, have attracted increasing interest due to their broad spectrum of biological activities.[2a–c] The most important step in the synthesis of these natural products is often the ring closure step to obtain the tetrahydrofuran. Several syntheses utilized 2-alkylidenetetrahydrofurans as key intermediates.[3–6] The multi-functionalities in 2-alkylidenetetrahydrofurans make them synthetically valuable. Useful methods have been developed to prepare these intermediates;[4] approaches include the cyclization and condensation of 6-hydroxy-1,3-hexanediones,[4a] the use of Reformatsky reaction between a zinc enolate and thionolactones[4b] and the palladium-catalyzed oxidative cyclization–alkoxycarbonylation of alkynes.[4c,d] A cyclization strategy using 1,3-dicarbonyl dianions or 1,3-bis-silyl enol ethers with 1,2-dielectrophiles was extensively utilized by the Langer group.[5]

Intramolecular oxy- and aza-Michael reactions have also become important strategies to prepare oxacycles and azacycles.[6] Activated alkenes have been widely used as Michael acceptors.[6a] The base-promoted intramolecular oxy-Michael reaction of electron-deficient allenes was shown to afford cyclization *via* the *endo*-mode.[6b] We have shown that guanidines such as 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) can be used as a strong Brønsted base to promote a variety of reactions.[7,8] We have also recently shown that a chiral di-*tert*-butyl bicyclic guanidine can catalyze the isomerization of alkynes to chiral allenes with high enantioselectivities.[7c] As a result of this previous work, we became interested in the development of intramolecular hetero-Michael reactions of allenes that were generated *in situ* by a base-catalyzed isomerization of alkynes.

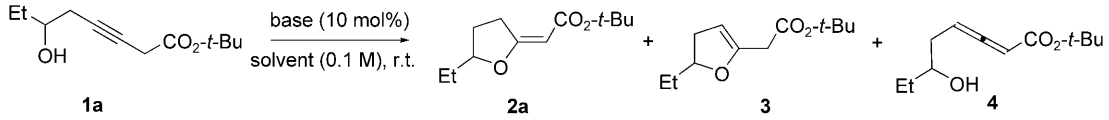
Results and Discussion

The 6-hydroxyalkynoate **1a** was conveniently prepared according to Fu's method (Scheme 1).[9] When the 6-hydroxyalkynoate **1a** was subjected to the isomerization conditions with 1 equivalent of triethylamine (Table 1, entry 1), two unusual cyclization prod-



Scheme 1. Preparation of 6-hydroxyalkynoate **1a**.

Table 1. Brønsted base-catalyzed tandem isomerization of alkynes.

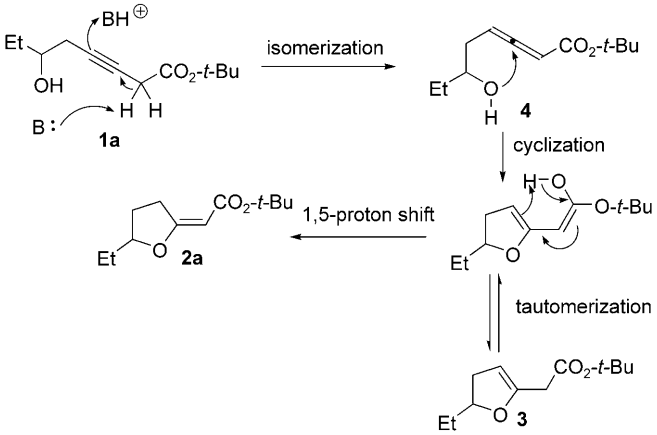


Entry	Base	Solvent	Time [h]	Conversions [%] (**2a**:**3**:**4**)[a]
1	Et_3N[b]	CH_2Cl_2	22	72 (7:33:60)
2	pyridine	CH_2Cl_2	18	0
3	DABCO	CH_2Cl_2	18	40 (35:17:48)
4	DBU	CH_2Cl_2	1.5	100 (2:1:0)
5	MTBD	CH_2Cl_2	2.5	100 (96:4:0)
6	TBD	CH_2Cl_2	0.5	100 (100:0:0)
7	TBD	THF	2.5	100 (55:20:25)
8	TBD	toluene	2.5	100 (84:16:0)

[a] Conversion and the ratio of **2a**, **3** and **4** were determined by ^{1}H NMR.
[b] 1 equivalent of base used.

ucts **2a** and **3** were obtained together with a small amount of allene **4**. Next, we investigated the use of different bases like pyridine, 1,4-diazabicyclo-[2.2.2]octane (DABCO) and 1,8-diazabicylo-[5.4.0]undec-7-ene (DBU) (entries 2–5). No product was observed when pyridine was used as the catalyst and the use of DABCO resulted in only 40% conversion. Complete reaction was observed with 10 mol% of DBU, 10 mol% of 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (MTBD) or 10 mol% of TBD. This is most likely due to their higher basicities. While complete reaction was observed for these three bases, the product distribution was different (entries 4–6). The highest amount of 2-alkylidenetetrahydrofuran **2a** was obtained using MTBD and TBD. The reaction with TBD was the fastest, which was completed in 0.5 hour. It was also found that different solvents such as THF and toluene resulted in different distributions of products.

We postulated that allene **4** is the common intermediate to both **2a** and **3**; and that **3** can be isomerized to **2a** under strongly basic conditions. We isolated allene **4** and tetrahydrofuran **3** separately and subjected each of them to reaction conditions similar to those of entry 6. In each case, both allene **4** and tetrahydrofuran **3** were fully converted to tetrahydrofuran **2a**. Thus, we proposed a mechanism for the formation of 2-alkylidenetetrahydrofuran **2a** (Scheme 2). The 6-hydroxyalkynoate **1a** first underwent the isomerization process to provide 6-hydroxyallenoate **4**, followed by an intramolecular Michael addition to give

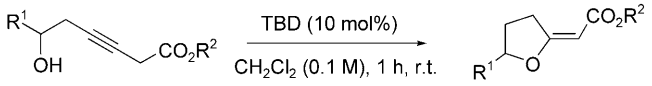


Scheme 2. Proposed mechanism for the tandem isomerization–oxy-Michael reaction.

a cyclized product **3**. Due to the acidity of the α-carbonyl proton, **3** was quickly isomerized to the more stable α,β-unsaturated ester, 2-alkylidenetetrahydrofuran **2a**. Density functional theory (DFT) calculations suggested that the cyclization step could be assisted by hydrogen bonding, and formation of the α,β-unsaturated ester could result directly from the enol intermediate *via* an intramolecular proton transfer (See Figure 1 for transition states).

A series of 6-hydroxyalkynoates **1a–g** were prepared (Table 2) and subjected to the optimized conditions for the tandem isomerization–oxy-Michael addition reaction. 2-Alkylidenetetrahydrofurans **2a–g**

Table 2. Substrate scope of tandem isomerization–oxy-Michael reaction.



1a – g **2a – g**

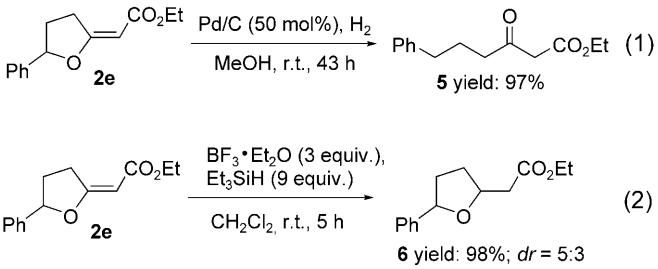
Entry	R^1	R^2	2	Yield [%][a]
1	Et	*t*-Bu	**2a**	94
2	Me	*t*-Bu	**2b**	92
3	H	*t*-Bu	**2c**	82
4	4-BrC_6H_4	*t*-Bu	**2d**	92
5	Ph	Et	**2e**	89
6	furan-2-yl	Et	**2f**	94
7	PhCH=CH	*t*-Bu	**2g**	92

[a] Isolated yield.

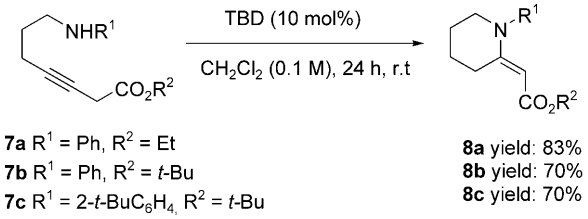
were obtained in excellent isolated yields and only the *E* diastereoisomers were observed. For all reactions, no dimer or oligomer, as a result of inter-oxy-Michael addition, was detected. Our attempt to generate oxacycles with ring sizes of four and six only resulted in the isomerization of the alkyne moiety to an allene in moderate yield. No cyclization product was observed. When the hydroxy group was replaced with an acid or a carbon nucleophile, it also resulted in allene as the only product.

5-Alkyl-substituted 2-alkylidenetetrahydrofurans can be easily reduced to their corresponding (tetrahydrofuran-2-yl)acetates with good diastereoselectivities under Pd/C hydrogenation conditions.[5a,b] However, when the 2-arylidenetetrahydrofuran **2e** was subjected to the Pd/C hydrogenation conditions, ethyl 3-oxo-6-phenylhexanoate **5**, a ring expanded keto ester was obtained with excellent yield [Scheme 3, Eq. (1)]. A different reduction method was required and different hydride sources were examined. Only Lewis acid-promoted silane reduction gave the functionalized tetrahydrofuran **6** with excellent yield [Scheme 3, Eq. (2)]. Attempts at improving the diastereoselectivity were not successful.

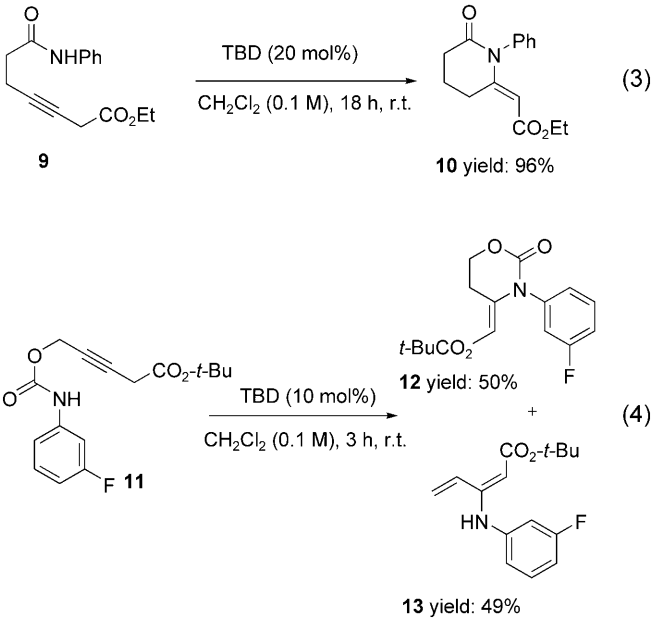
We were interested to extend the concept of tandem isomerization Michael reaction to other nucleophiles, especially, nitrogen ones. Alkynylamines



Scheme 3. Reduction of 2-arylidenetetrahydrofuran **2e**.



Scheme 4. Tandem isomerization–aza-Michael reaction of alkynylamines.



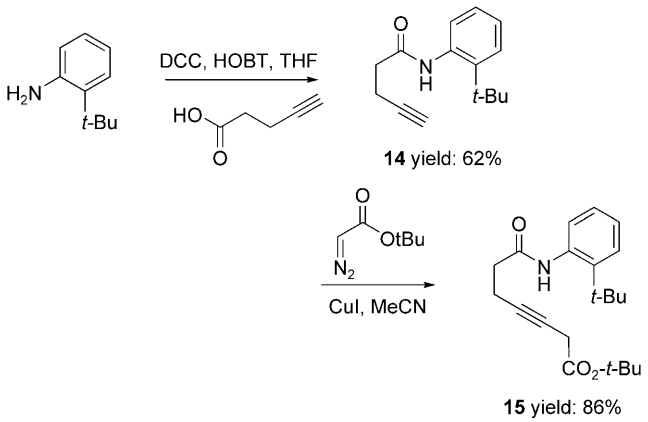
Scheme 5. Application for alkynylamides and alkynyl carbamates.

7a–c (Scheme 4) were prepared using the same approach as in Scheme 1. They were subjected to the optimized conditions in Table 2. A slightly longer reaction time was used to make sure that complete reactions were achieved as the products **8a–c** were non-separable from their corresponding starting materials, the alkynylamines **7a–c**. Piperidine derivatives **8** were achieved in good yields. When we subjected alkynylamine **7a** to the same reaction conditions for one day without the presence of the base, TBD, starting material was fully recovered and no other product was obtained.

In a similar approach, the intramolecular aza-Michael reaction of alkynylamide **9** provided lactam **10** in excellent yield after an overnight reaction using 20 mol% of TBD [Scheme 5, Eq. (3)]. Carbamate **11**, derived from a 5-hydroxyalkynoate, underwent a tandem isomerization–aza-Michael reaction to give a 6-membered oxazolidinone **12** [Scheme 5, Eq. (4)]. However, a significant amount of a side product was obtained and determined to be a conjugated imide **13**.

This imide **13** was very unstable and decomposed quickly at room temperature. The formation of imide **13** from oxazolidinone **12** may involve an isomerization–decarboxylation mechanism (see the Supporting Information for details). Alkynylamines and alkynylamides that may lead to a pyrrolidine were not studied due to the difficulty in obtaining the required starting materials.

We realized that lactam **10** can exist as atropisomers if the aryl protecting group has a large *ortho* substitution that restricts the rotation around the N–C bond. We have previously studied the kinetic as well as thermodynamic parameters of the rotational barrier of atropisomeric *N*-arylmaleimides.[10a] Atropisomeric lactams have received much attention recently as novel chiral molecules with potential applications in asymmetric synthesis.[10a–d] Amide **15** was prepared using a similar strategy as previously discussed (Scheme 6) and this amide was used to test the possibility of obtaining atropisomeric lactam directly from



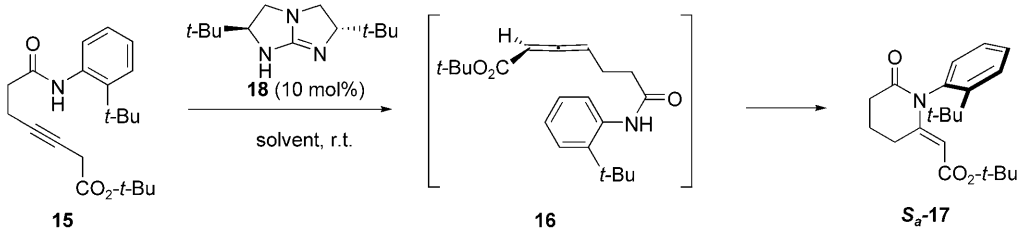
Scheme 6. Preparation of *tert*-butyl 7-(2-*tert*-butylphenylamino)-7-oxohept-3-ynoate **15**.

the chiral Brønsted base-catalyzed asymmetric tandem isomerization–cyclization. The chiral guanidine-catalyzed[11] reaction and subsequent purification led to axially chiral lactams **17** (Table 3). High enantioselectivities of lactam **17** were observed when the solvents used for the reaction were ether (85% *ee*) or THF (89% *ee*). Efforts to prepare other atropisomeric six-membered lactams were not successful due to the difficulty in preparing suitable alkynes as the starting material. Similarly, efforts to prepare different ring sizes were also not too successful. The alkynes were unable to complete the intramolecular Michael reactions and provided the corresponding enantioenriched allenes, for which the absolute configurations were determined by the Lowe–Brewster rule[12] (Scheme 7).

The observation that allenes were obtained when **19**, **21**, **23**, **24** and **25** were used as reactants suggests that the formation of $\boldsymbol{S_a}$**-17** from **15** proceeds *via* allene **16** with the same configuration as the other allenes. Difficulty in obtaining single crystals for $\boldsymbol{S_a}$**-17**, together with the lack of heavy atoms in $\boldsymbol{S_a}$**-17**, which could impede absolute configuration determination *via* single crystal X-ray diffraction[13] motivated us to derive the absolute configuration *via* theoretical approaches. Reliable specific optical rotation values can be calculated from density functional theory (DFT) by considering thermally accessible conformations and with judicious choice of the basis set and functional coupled with solvation model to account for solvent effects.[14] The specific optical rotation for the $\boldsymbol{S_a}$**-17** configuration calculated as −57.8, which agrees well with the −64.1 that was obtained experimentally.

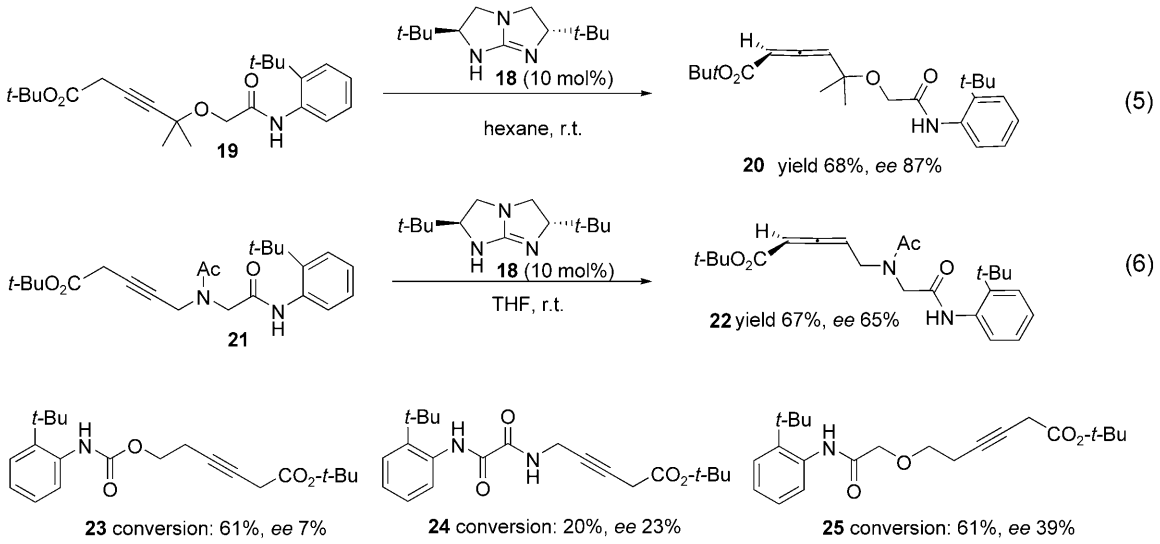
In addition, we have investigated the mechanism *via* DFT calculations. The intramolecular Michael reactions will translate the axial chirality of the allene to the atropisomeric chirality. The activation barriers for the relevant pathways are given in Figure 1. Based

Table 3. Chiral guanidine-catalyzed tandem isomerization–Michael reaction for the synthesis of axially chiral lactams.



Entry	Solvent	Time [days]	Yield [%][a]	*ee* [%][b]
1	DCM	4	68	60
2	toluene	3	60	81
3	hexane	2	75	65
4	diethyl ether	2	74	85
5	THF	3	67	89

[a] Isolated yield.
[b] Determined by HPLC



Scheme 7. Enantioselective isomerization of alkynes to allenes.

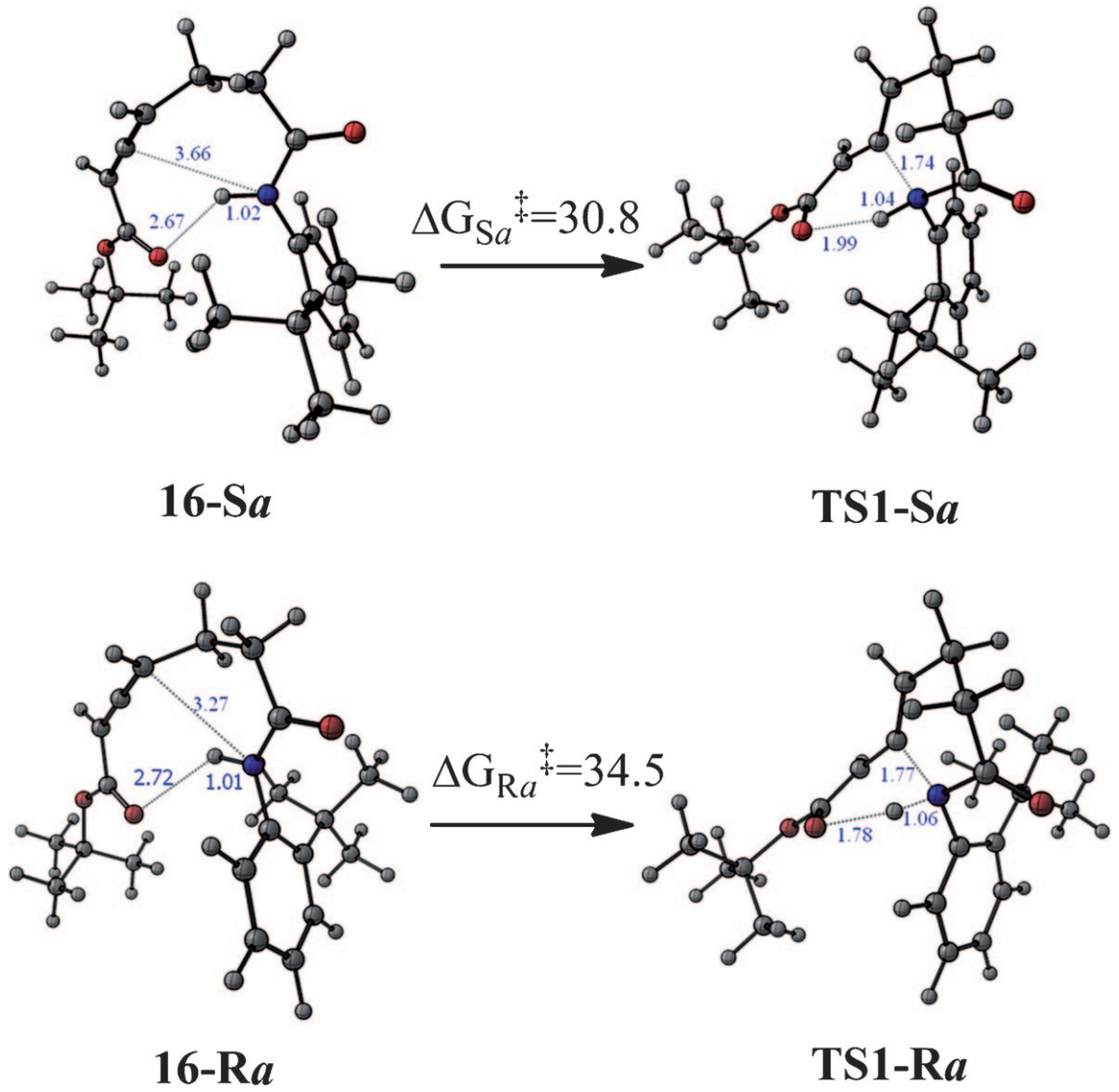


Figure 1. Enantioselectivity step (Gibbs free energy difference given in kcal mol^{-1}).

on this mechanism, the formation of S_a product is predicted to be more favourable than the R_a product. The Gibbs free energy of activation difference ($\Delta G^{\neq}$) of the pathways leading to the S_a lactam is 3.4 kcal mol^{-1} lower in Gibbs free energy than the pathway leading to the R_a lactam, which is consistent with the high *ee* observed experimentally.[16]

Conclusions

In conclusion, we have found that a Brønsted base-catalyzed tandem isomerization–Michael reaction can be used to form useful heterocycles under mild conditions. This efficient method was applied to the synthesis of various functionalized 2-alkylidenetetrahydrofurans with excellent yields. Tandem isomerization–aza-Michael reactions with alkynylamines, alkynylamide and alkynyl carbamates led to interesting piperidines, lactams and oxazolidinones. An axially chiral lactam was also obtained with high enantioselectivity when a chiral guanidine was used as the catalyst.

Experimental Section

Eperimental Protocol for Brønsted Base-Catalyzed Tandem Isomerization Reactions

To a clear and dry vial, *tert*-butyl 6-hydroxyoct-3-ynoate **1a** (21 mg, 0.1 mmol), a stirring bar and anhydrous CH_2Cl_2 (0.9 mL) were added in this sequence. After stirring at room temperature for a while, TBD (1.4 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (0.1 mL) was added to the mixture in one portion. After the reaction was completed in 1 hour, the reaction mixture was concentrated and loaded onto a short silica gel column, followed by flash chromatography. Product **2a** was obtained as colorless oil;yield: 20 mg (94%).

Computations

Density functional theory (DFT) calculations were performed using the *Gaussian 09* program package.[17] Geometries were optimized with RB3LYP[18]/6-31+G(d,p)[19] and CPCM[20] solvation model to simulate tetrahydrofuran as the solvent medium. The nature of each stationary point was characterized by normal coordinate analysis. Single-point energy calculations with M06-2X functional, which is expected to confer a more accurate treatment of medium-range correlation,[21] were performed on CPCM/RB3LYP/6-31+G(d,p) optimized geometries using a more extended basis set: 6-311+G(2df,2p)[22] with CPCM solvation model to simulate the effect of tetrahydrofuran as solvent. The performance of single-point energy calculations with M06-2X on B3LYP geometry has been evaluated by Houk et al.[23] The difference in activation barrier given in the Results and Discussion is based on the Gibbs free energy difference derived from the sum of electronic energy from CPCM/M06-2X/6-311+G(2df,2p), and thermal correction to Gibbs free energy from vibrational frequencies calculation at CPCM/RB3LYP/6-31+G(d,p). For specific optical rotation calculation of ***S*$_a$-17**, we adopted a method similar to that of Grajewska et al.,[14] with the exception of the method used to generate the conformations required, which was performed using *Accelrys Discovery Studio*.[24]

Supporting Information

Experimental procedures, characterization and spectroscopic data (PDF), together with cartesian coordinates, relevant energies of all stationary points (minima and transition states), complete citation to ref.[17], and a detailed description of the computational methods are available as Supporting Information.

Acknowledgements

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