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Synthesis of Substituted Morpholines Using Stereodivergent Aza-Michael Reactions Catalyzed by Brønsted Acids

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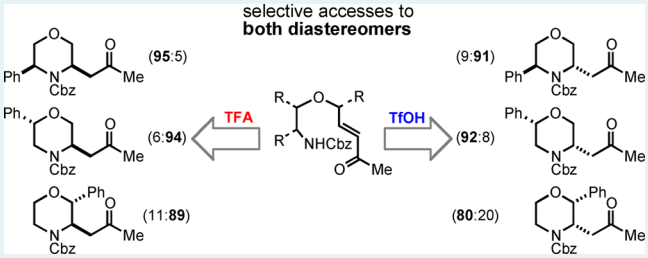
Supporting Information

ABSTRACT: A diastereoselective intramolecular aza-Michael reaction between N-Cbz carbamates and enones was studied. The investigation revealed that Brønsted acids with different strengths produce different diastereomers. The catalysts TfOH and TFA were used to generate differential outcomes in the aza-Michael reaction.

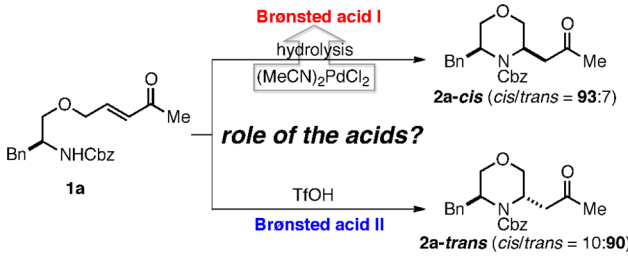


KEYWORDS: *Brønsted acid, aza-Michael, diastereoselective, morpholine, heterocycle*

Substituted morpholines are highly represented among small molecules that are biologically and therapeutically relevant, including many natural products.[1] Morpholine scaffolds have also been widely utilized in the agrochemical industry for their antibacteriacidal and antifungicical properties,[2] and as chiral auxiliaries in asymmetric synthesis.[3] The predominant method for the preparation of chiral C-substituted morpholines employs amino acids as precursors owing to the availability of such starting materials from the chiral pool.[4] However, toward the preparation of more stereodiverse substituted analogues, the generation of additional stereogenic centers from these precursors within the morpholine skeleton has been limited.[5] Given the prevalence and importance of this family, we sought a general methodology to produce stereochemically and structurally diverse morpholines for biological evaluation. Herein, we report a facile access to both disastereomers of various substituted morpholines in an aza-Michael reaction using Brønsted acids with different acidity.

The aza-Michael reaction has been widely applied for C−N bond formation, especially in the preparation of biologically active small molecules.[6] Enantioselective aza-Michael reactions promoted by organocatalysts and transition-metal complexes have been extensively studied.[7] However, despite steady advances in this area,[8] progress toward diastereoselective intramolecular aza-Michael reactions has lagged, mainly because of the difficulty in achieving stereochemical control.[9] We envisioned that the ability to obtain either diastereoisomer of *di*-or *tri*-substituted morpholines from a common precursor would be highly attractive because of efficiency. Typically a chiral catalyst and its antipode are used to achieve this goal. However, we have previously demonstrated that the achiral $(MeCN)_2PdCl_2$ and TfOH, could effectively promote the intramolecular aza-Michael reaction diastereoselectively to give the *cis*- or *trans*-isomers of morpholines, respectively (Scheme 1).[10]

Scheme 1. Diastereoselective Intramolecular aza-Michael Addition by Different Achiral Catalysts



We became interested in probing the origins of the stereoselectivity of these reactions toward the generation of other stereodiverse morpholines. Although both catalysts had been previously reported to catalyze the aza-Michael reaction, there were no studies detailing issues related to stereoselectivity.[11] Moreover, in the case of Pd(II) catalysis, the reaction mechanism was a subject of debate. One argument favors the palladium species serving as a Lewis acid to activate the enone carbonyl group or the C=C bond.[11d,11e] An alternative explanation, based on the fact that Brønsted acids can also catalyze aza-Michael reactions, is that the operative catalyst is a proton generated during transition-metal hydrolysis resulting from adventitious water in the reaction system. Spencer and co-workers reported in

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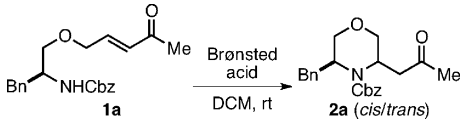
2006 a detailed study supporting the hydrolysis theory.[11c] Following their studies, we also performed water titration experiments as well as the addition of acid scavengers to the reaction.[12] The outcomes from both experiments were consistent with Spencer's observations, suggesting that catalysis by protic acid is the dominant pathway for the Pd(II) reaction (Scheme 1).

With the knowledge that protic acid functions under both conditions and leads to opposing stereoselectivity of 3,5-disubstituted morpholines, we explored this phenomena more extensively. The results of different Brønsted acids are summarized in Table 1. The

Table 1. Brønsted Acids in aza-Michael Reaction



entry	Acids (0.1 eq)	Time (h)	Yield (%)	*d.r.*
1	**TfOH**	0.25	93	13:87
2	Tf_2NH	0.25	91	15:85
3	HBr[c]	3	81	38:62
4	HBF_4[d]	2	93	24:76
5	**TFA**	60	79	>95:5
6	TFA (0.2 eq.)	24	86	95:5
7	TFA (0.5 eq.)	7	89	88:12
8	TFA (1.0 eq.)	5	89	85:15
9	AcOH (solv.)	48	<5	--:--

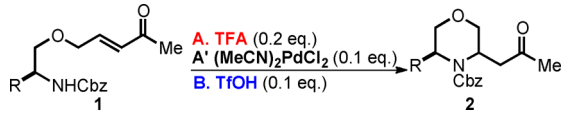
[a]NMR yield. [b]Based on crude NMR. [c]30% AcOH solution. [d]50% aqueous solution, 20% MeCN as solvent.

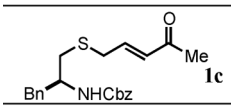
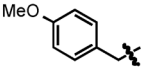
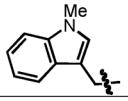
intramolecular aza-Michael reaction reached nearly full conversion within 15 min when strong Brønsted acids (TfOH or Tf_2NH) were used (Table 1, entry 1, 2). The diastereoselectivity favored the *trans* isomer with a diastereomer ratio (*d.r.*) of 13:87 (*cis*/*trans*). When HBr (30% AcOH solution) and HBF_4 (50% in water) were used, longer reaction times were required with lower selectivity, but still favoring the *trans* isomer (Table 1, entry 3, 4).

In the case of TFA (0.1 equiv.), the reaction slowed significantly (79% conversion in 60 h). However, the *d.r.* was over 95:5 favoring the *cis* isomer (Table 1, entry 5). Higher TFA concentrations led to an increased reaction rate, but the selectivity was diminished (Table 1, entry 6, 7). Weak acids such as AcOH did not catalyze the aza-Michael reaction to any extent over 48 h even when used as solvent (Table 1, entry 8). The Pd(II) complexes with different ligands or counteranions were also tested and compared, which provided strong supporting evidence to the hydrolysis theory. Complexes with more electron-donating ligands did not catalyze the reaction likely because of attenuation of the hydrolysis process whereas less electron donating ligands did catalyze the reaction providing a range of diastereoselectivities (see Supporting Information).[12] Combining the results from different Pd(II) complexes and acids, we concluded that the acidity of the Brønsted acid is the key factor controlling the diastereoselectivity in the intramolecular aza-Michael reaction between the Cbz carbamate and enone. Accordingly, we selected TfOH and TFA as catalysts to explore the scope of this complementary diastereoselectivity.

Substrates in our previous report were revisited using TFA as a catalyst. Identical (or better) *cis* selectivity was obtained compared to $Pd(MeCN)_2Cl_2$ (Table 2 1a, 1b). Moreover, for a substrate found to poison the Pd(II) catalyst (Table 1c), the TFA condition provided good yield and high *cis* selectivity.

Table 2. Diastereoselectivity Comparison between $Pd(MeCN)_2Cl_2$, TFA-and TfOH-Catalysis[a]



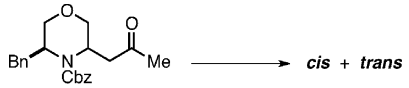
R		Condition	yield (%)	*cis*:*trans*
Bn	**1a**	**A**	90	**95**:5
		A′	89	**93**:7
		B	93	9:**91**
Ph	**1b**	**A**	93	**95**:5
		A′	95	**94**:6
		B	91	12:**88**
	**1c**	**A**	81	**89**:11
		A′	--	--
		B	91	7:**93**
	**1d**	**A**	83	**95**:5
		A′	90	**92**:8
		B	95	7:**93**
	**1e**	**A**	71	**72**:28
		A′	63	**70**:30
		B	64	25:**75**
	**1f**	**A**	91	**95**:5
		A′	87	**90**:10
		B	94	7:**93**
t-Bu	**1g**	**A**	53	43:57
		A′	58	46:54
		B	84	23:**77**

[a]See Supporting Information for reaction details.

More complex aza-Michael precursors were also prepared and tested (Table 1 1d−1f), with similar reactivity and selectivity observed. For the *t*-Bu substituted precursor **1g**, the reaction rates were dramatically decreased under both conditions. The TfOH-catalyzed reaction gave 84% yield (*cis*/*trans* 23:77) at room temperature over 8 h, while treatment with TFA provided a modest 53% yield after 4 days, slightly favoring the *trans* isomer.

To probe the reaction mechanisms, both purified *cis* and *trans* isomers of **2a** were isolated and resubjected to the reaction conditions at room temperature (Table 3). For **2a-*cis***, no detectable

Table 3. Lack of Reversibility with Both Diastereoisomers



	condition[a]	recovery	*d.r.*
2a-*cis*	**TFA** (0.2 eq.)	>95	>**98**:2
	TfOH (0.1 eq)	85	>**98**:2
2a-*trans*	**TFA** (0.2 eq.)	>95	<2:**98**
	TfOH (0.1 eq)	78	13:**87**

[a]Room temperature with 0.2 M concentration of **2a**. [b]NMR yield. [c]Determined by crude NMR after 24 h.

trans isomer was observed under both TFA and TfOH conditions; however, minor decomposition was observed using stronger Brønsted acid. Resubjection of **2a-*trans*** did not result in conversion to the *cis* isomer under TFA conditions; however,

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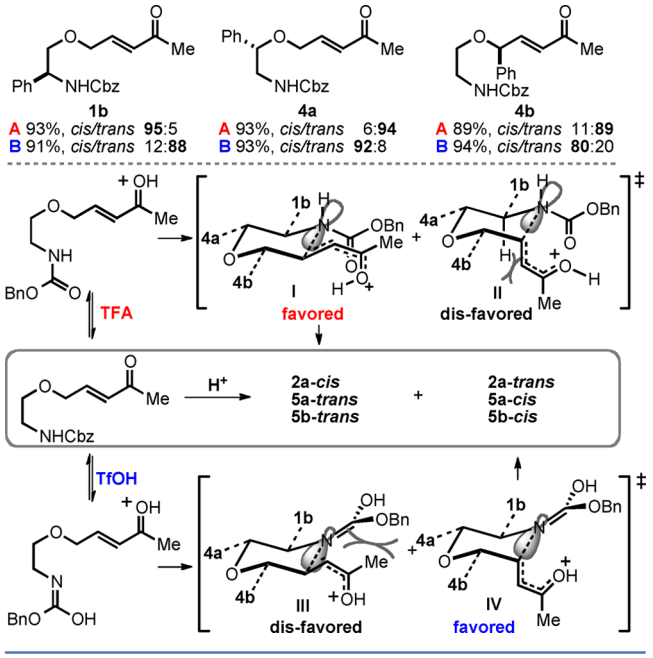
a 13:87 *d.r.* (*cis*:*trans*) was observed with 78% recovery under TfOH condition over 24 h at room temperature. These data indicate that both TFA and TfOH catalyzed reactions are largely under kinetic control. Therefore, different transition states account for the preferences in diastereoselectivity.

We next sought to examine the methodology toward preparing morpholines with other substitution patterns. Accordingly, substrates having different regiochemical and stereochemical configurations were prepared and tested under both conditions (Scheme 2). Interestingly, when the stereogenic center was moved

Scheme 2. Mechanistic Rationale of the Diastereoselective Intramolecular aza-Michael Addition

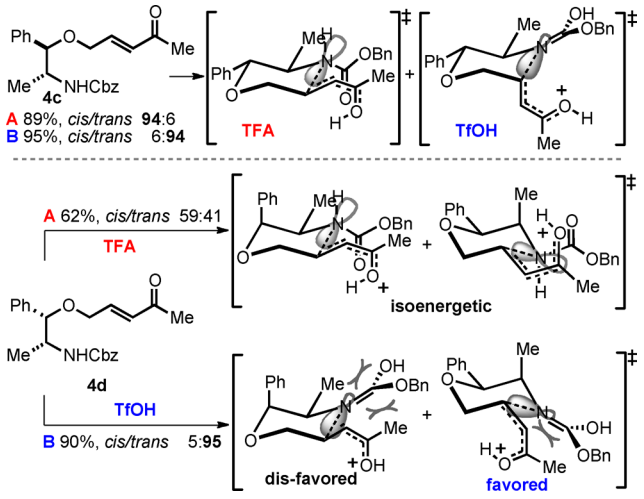


adjacent to the oxygen (**4a**), the diastereoselectivity was reversed from the previous trend. Treatment with TFA gave the *trans* isomer as the dominant product, while TfOH was selective toward the *cis* isomer. Substrate **4b** gave similar selectivity compared to **4a**, although with slightly diminished selectivity. Taking these observations into account, we propose that the intramolecular aza-Michael reaction between carbamate to enone proceeds through an early chairlike transition state (Scheme 2). When employing TFA as a catalyst, in the case of **1a**, the lower energy chairlike conformation places the substitutents in equatorial positions. Because of the lower acidity of TFA, the proton may serve only to activate the electrophilic enone. A face-on addition of the nitrogen p-orbital of the nucleophilic carbamate can engage the lowest unoccupied molecular orbital (LUMO) of the enone positioned equatorially, providing the *cis* products (Scheme 2 I vs II).

Alternatively, under TfOH treatment, we suggest on the basis of NMR probing experiments that the carbamate carbonyl is protonated and tautomerized into a carboimidate intermediate.[13] A fully sp^2 hybridized nitrogen nucleophile undergoes a head-on addition to the enone. To minimize the *pseudo*-$A^{(1,3)}$ repulsion[14] between the carboimidate and the electrophile (Scheme 2 III), the enone may adopt an axial position, leading to the *trans* isomer (Scheme 2 IV). In the case of a phenyl substitution adjacent to nitrogen, an equatorial orientation induces a *pseudo*-$A^{(1,3)}$ interaction under the TfOH conditions, which enforces the alternative chair transition state with the phenyl disposed axially and the enone in the *pseudo*-equatorial position. Alternatively, we cannot rule out that the transition state may proceed through a twisted-boat conformation to minimize the repulsions.[15] Results from substrate **4a** are also in accord with the proposed model, having the phenyl group on the equatorial position in transition states under both conditions. In the case of **4b**, TFA treatment results in similar selectivity favoring *trans* isomers, and TfOH conditions yield slightly diminished selectivity favoring the *cis* isomer. This might be due to steric repulsion between the equatorial phenyl group and the axial enone (Scheme 2 IV). These studies demonstrate that the aza-Michael reaction can be invoked to generate both stereoisomers of 3,5-, 2,5-, and 2,3-disubstituted morpholine ring systems.

We also studied the diastereoselective aza-Michael reactions in the context of generating trisubstituted morpholines. The transition-state model proposed above is also applicable to substrates prepared from norephedrine (Scheme 3). As a combination of **1b** and **4a**,

Scheme 3. Further Investigation of Steric Effect on Diastereoselective aza-Michael Reaction



both substitutents in **4c** are presumably in the equatorial positions, which should reinforce the diastereoselectivity based on the proposed model. As expected, high yield and excellent diastereoselectivity are obtained under both TFA and TfOH conditions. In the case of **4d** using TFA, diminished chemical yields and poor diastereoselectivity resulted. This may be attributed to the steric effects raised by the *pseudo*-axial substituent in the proposed iso-energetic transition states. However, under TfOH conditions, good yield and excellent *trans* selectivity are achieved. As shown in Scheme 3, to avoid the possible double *pseudo*-$A^{(1,3)}$ and *pseudo*-axial interactions, the *trans* isomer is favored in the proposed chairlike model.[16] Therefore, with the exception of one instance, the diasteromeric 2,3,5-trisubstituted morpholines were produced in excellent yield, demonstrating the broad utility of this reaction methodology. Taken together, this study represents the most general construction of substituted morpholines arising from a common bond forming strategy.

In conclusion, we have demonstrated a robust stereodivergent strategy leading to substituted morpholines employing Brønsted acid catalyzed intramolecular aza-Michael reactions. Previously examined Pd(II) complexes were found to promote the reaction by hydrolysis to release protons as the active catalysts. Furthermore, the acidity of Brønsted acids was determined to influence the diastereoselectivity of the reaction. In the generation of 3,5-disubstituted

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morpholines, higher acidity (TfOH) yields the *trans* isomer, while relatively lower acidity (TFA) provides the *cis* isomer. Using the same acids, the selectivities were opposite for the generation of the corresponding 2,5-and 2,3-disubstituted morpholines. The catalysts were extended to 2,3,5-trisubstituted morpholines with excellent diastereoselectivity. Finally, the rationale of the stereochemical outcomes of these reactions led to a mechanistic model of the acidity-controlled diastereoselectivity. The transition state model generated from these studies suggests a possible means to access other types of aza-heterocycles with tunable diastereoselective control, and our efforts in this direction will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details are provided as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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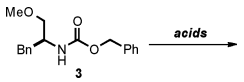
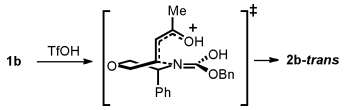
(12) See Supporting Information for the titration of water experiment and detailed screening of different Pd(II) complexes.

(13) Carbamate **3** was prepared for an NMR study to probe the differences between TfOH and TFA conditions. See Supporting Information for details.

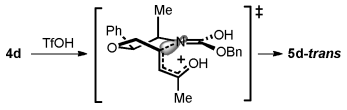


(14) For review on $A^{(1,3)}$ interaction, see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.

(15) Based on the energy difference of a twisted-boat conformation (5.3 kcal/mol in cyclohexane) and the $A^{(1,3)}$-strain (~3.4−4.7 kcal/mol), the proposed chairlike transition state should be lower in energy. However, under TfOH conditions, the possibility of twisted boat conformation could not be excluded, as shown below.



(16) A twisted boat conformation is also possible in this case, leading to the *trans* isomer.



■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, the version of this paper that was published ASAP on March 11, 2013, was missing the graphic with reference 16. The corrected version was reposted March 15, 2013.