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Diastereoselective Control of Intramolecular Aza-Michael Reactions Using Achiral Catalysts

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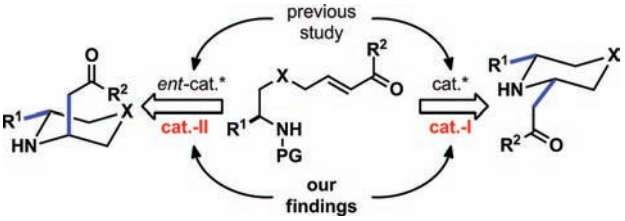
ABSTRACT



An intramolecular aza-Michael reaction with a Cbz carbamate and an enone is reported to result in 3,5-disubstituted nitrogen-containing heterocycles. Either *cis* or *trans* isomers were obtained selectively using chiral substrates and an achiral Pd (II) complex or strong Brønsted acid catalysis. A range of substrates undergoes these selective transformations. Functionalization of the resulting products yielding bicyclic heterocycles is also demonstrated.

Stereochemical diversity is a useful feature of compound libraries since it can yield stereochemical structure−activity relationships.[1] The introduction of stereogenic elements within a chiral substrate has been catalyzed selectively to provide either diastereomer in a number of studies.[2] However, chiral catalyst-based control of diasteroselectivity is often challenging due to the difficulty of overcoming the intrinsic stereochemical preference of the chiral substrates. Here, we describe the use of *achiral* transition-metal- and Brønsted acid-based catalysts in intramolecular aza-Michael reactions that yield either *cis*- or *trans*-disubstituted nitrogen-containing heterocycles.

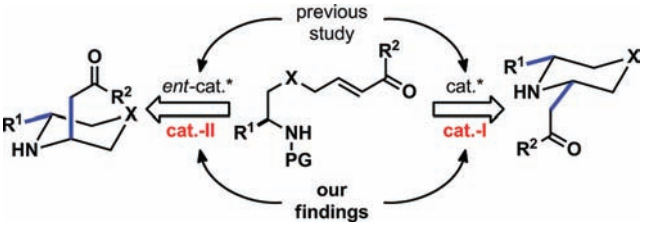


Figure 1. Diastereoselective intramolecular aza-Michael addition.

The aza-Michael reaction has been used for C−N bond formation in the preparation of a variety of biologically active small molecules.[3] Enantioselective syntheses promoted by organocatalysts and transition-metal complexes

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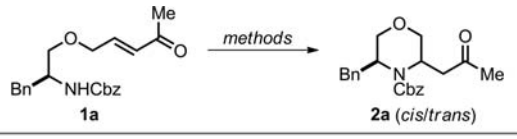
have been extensively studied.[4] The intramolecular aza-Michael reaction has also been useful, yielding natural products and pharmaceutically relevant nitrogen-containing heterocyclic small molecules.[5] While the catalytic enantioselective aza-Michael reaction has been demonstrated, the diastereoselective variant yielding one or the other of two possible stereoisomers is less common. A common strategy entails treating chiral substrates with chiral catalysts.[6] Antipodes of the catalyst can, in principle, yield either diastereoisomer via "matched" or "mismatched" pathways[7] (Figure 1). An alternative approach is the use of distinct achiral catalysts to access different diastereoisomers through distinct mechanistic pathways.[2a,b]

Scheme 1. Intramolecular Aza-Michael Addition of an Amino Alcohol Derived Carbamate-Tethered Enone[8]



1a **2a** (*cis*/*trans*)

	condition	result
A	$BF_3 \cdot OEt_2$	decomposition
B	organocatalysts	no reaction
C	KO^{t}Bu (1.0 equiv), THF, - 78 °C, 8 h	54% yield, *cis*/*trans* ~ 2:1
D	**$(MeCN)_2PdCl_2$ (0.1 equiv), DCM, rt, 5 h**	**89%** yield, *cis*/*trans* **93**:7
E	Pd(II), chiral phosphine ligands	--% yield, *cis*/*trans* --:--
F	Pd(II), chiral pyridine ligands	>15 % yield, *cis*/*trans* --:--
G	Pd(II), chiral phosphate ligands	-- % yield, *cis*/*trans* --:--

Our investigation started from the Cbz carbamate-tethered enone **1a**, which was easily prepared from L-phenylalinol.[9] We initially investigated reported methods of intramolecular aza-Michael reactions.[10] Strong Lewis acids such as $BF_3 \cdot OEt_2$ led to decomposition of the starting material (Scheme 1A). Organocatalysts including chiral proline derivatives and cinchona alkaloids were also examined. Although these catalysts were reported to be effective for enal electrophiles with high enantioselectivity, no product formation was observed for the enone substrate **1a** (Scheme 1B). Under basic conditions using KO-*t*-Bu (1.0 equiv), 3,5-disubstituted morpholine **2a** was obtained in 54% yield and a moderate 2:1 dr, favoring the *cis* isomer; however, decomposition was also detected (Scheme 1C).

Studies performed by Spencer,[11] Kobayashi,[12] and others[13] demonstrate that transition-metal complexes can catalyze intermolecular aza-Michael reactions. When $(MeCN)_2PdCl_2$ (0.1 equiv) was used in dry DCM, Michael addition was achieved in 5 h in 89% yield. Moreover, the diastereoselectivity increased to 93:7, favoring the *cis* isomer (Scheme 1D). Although we imagined that the *trans* isomer might be obtained by applying chiral ligands to palladium(II), this proved not to be the case. Chiral phosphine ligands[14] (BINAP, "Trost ligand") significantly diminished the rate of the reaction (Scheme 2E), and pyridine ligands[15] (BOX, PyBOX) promoted no more than 15% conversion over 48 h at room temperature (Scheme 1F). The Pd(II) chiral counteranion strategy[16] was also examined without encouraging results (Scheme 1G).

The mechanism of Pd(II) complex catalyzed aza-Michael reactions may involve enone activation by either a Pd(II) species[11,13] or a proton resulting from hydrolysis of the transition-metal complex.[17] Indeed, strong Brønsted acids are known to catalyze aza-Michael reactions and are superior to Pd(II) complexes in some cases.[18] Prior to testing chiral Brønsted acids (thioureas,[19] chiral phosphoric acids,[20] and chiral *N*-triflylphosphoramides[21]) (Scheme 2A), we performed a control experiment using triflic acid (TfOH). To our surprise, a catalytic amount of TfOH (0.1 equiv) in DCM provided **2a** in 93% yield in 15 min with reversed diastereoselectivity (*cis*/*trans* 15:85) (Scheme 2B) in relation to Pd(II) catalysis (*cis*/*trans* 93:7). Lowering the temperature to −20 °C resulted in improved diastereoselectivity (*cis*/*trans* 9:91) (Scheme 2C). Thus, different achiral catalysts

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(8) See the Supporting Information for more detailed screening.

(9) See the Supporting Information for detailed syntheses of all the substrates.

(10) For $BF_3 \cdot OEt_2$ catalysis, see: Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700. For prolinol silylether catalysis, see: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283. For basic conditions, see:Sudhakar, N.; Srinivasulu, G.; Rao, G. S.; Rao., B. V. *Tetrahedron: Asymmetry* **2008**, *19*, 2153.

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(16) For example, see: Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

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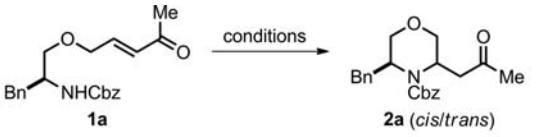
Scheme 2. Diastereoselective Intramolecular Aza-Michael Addition Catalyzed by Brønsted Acid



	condition	result
A	Chiral Brønsted acid catalysts	not tested
B	TfOH (0.1 equiv), DCM, rt, 15 min	93% yield, *cis*/*trans* 15:**85**
C	**TfOH (0.1 equiv), DCM, -20 °C, 5 h**	**92**% yield, *cis*/*trans* 9:**91**

can switch the diastereomeric preference to yield either *cis* or *trans* 3,5-disubstituted morpholines selectively.[22]

In order to determine the generality of these findings, additional chiral substrates were prepared and subjected to both conditions (Table 1). A variety of substituents on the amino alcohol was tolerated, providing up to over 10:1 selectivity for both C-5 epimers and favoring either *cis* or *trans* isomers. Subtle differences were observed (comparing **1a**, **1b**, and **1c**), when different enone substituents were present at the C-5 position of morpholines. Bulky groups at the C-3 position yielded slightly improved diastereoselectivity (comparing **1a**, **1f**, **1h**, and **1l**). The lowest degree of selectivity was observed with methyl and methyl ketone substituents on the C-3 and C-5 positions (**1j**).

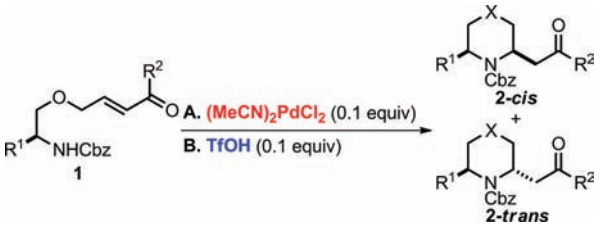
The enal substrate **1d** also underwent this reaction, although with moderate yields and diastereoselectivities. The α,β-unsaturated ester **1e** gave only a trace amount of product under both conditions, which is likely due to its nature as a weak Michael acceptor. However, removing the *N*-Cbz group promoted the aza-Michael reaction in situ to give the *cis* product in a 97:3 ratio. When the serine derivative **1m** was examined, Pd(II) catalysis gave moderate selectivity (*cis*/*trans* 62:38), while the TfOH catalysis also provided predominantly the *cis* isomer (*cis*/*trans* 76:24).

The preparation of nitrogen-containing heterocycles other than morpholines was also investigated. Different linkers were installed on the six-membered ring and subjected to the reaction conditions. The results are summarized in Scheme 3.

Both amino ester **3a** and amino amide **3b** did not convert to the expected products under either of the two catalysis conditions. We determined that the dipeptide **3c** is an effective substrate under both reaction conditions, and excellent yields were obtained. However, the stereochemical outcome was different than that observed with other substrates. The Pd(II) catalyst provided the *trans* isomer predominantly (*cis*/*trans* 26:74), while the Brønsted acid catalysis slightly favored the *cis* isomer (*cis*/*trans* 57:43). Taken together with the results of serine derivatives (**1l** and **1m**), we rationalize that the extra carbonyl group(s) may influence the stereochemical outcomes under both conditions. Substrate **3d** gave similar reactivity and stereochemical outcomes as the morpholines under both conditions. The orthogonally protected nitrogens contained within these piperazine products can be differentially functionalized.

Sulfide and sulfone linkers were also prepared. Excellent yield (91%) and selectivity (*cis*/*trans* 7:93) were obtained for sulfide **3e** using the TfOH conditions. However, the Pd(II) complex failed to catalyze the reaction, mainly due to the strong coordination of sulfur to Pd(II) species. The reaction of sulfone substrate **3f** proceeded with excellent yield and diastereoselectivity under both Pd(II) and Brønsted acid catalysis conditions,[24] but the Brønsted acid catalysis also provided the *cis* isomer as the major product.

Table 1. Diastereoselective Intramolecular Aza-Michael Addition To Achieve Both *Cis* and *Trans* Isomers[a]



R^1	R^2		conditions[b]	yield[c] (%)	dr[d] (*cis*:*trans*)
Bn	Me	**1a**	A	89	93:7
			B	93	9:91
	Et	**1b**	A	90	92:8
			B	91	9:91
	Ph	**1c**	A	86	90:10
			B	89	12:88
	H	**1d**	A	71	83:17
			B	64	21:79
	OMe	**1e**	A	--	--:--
			B	--	--:--
			C[e]	87	97:3
i-Pr	Et	**1f**	A	90	94:6
			B	85	14:86
	Ph	**1g**	A	89	93:7
			B	81	17:83
Ph	Me	**1h**	A	94	94:6
			B	91	12:88
	Ph	**1i**	A	88	93:7
			B	86	17:83
Me	Me	**1j**	A	95	69:31
			B	91	25:75
	Ph	**1k**	A	89	86:14
			B	90	19:81
Cy	Me	**1l**	A	92	91:9
			B	95	11:89
CO_2Me	Me	**1m**	A	91	62:38
			B	93	76:24

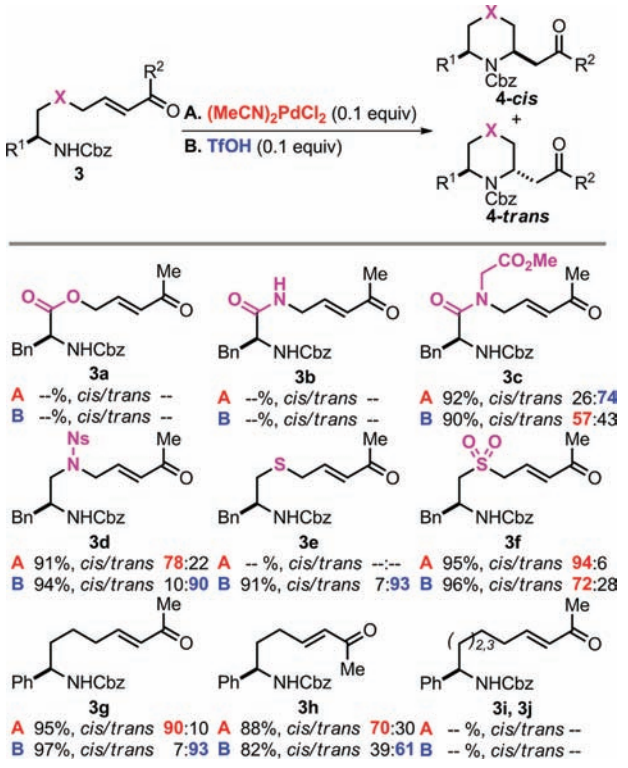
[a] The relative stereochemistry of both *cis* and *trans* isomers were determined by NOE after Cbz removal and X-ray structure determination after the following transformations. [b] Conditions: (A) $(MeCN)_2PdCl_2$ (0.1 equiv), dry DCM (0.1 M), rt, 4−7 h; (B) TfOH (0.1 equiv), dry DCM (0.1 M), −20 °C, 3−5 h. [c] Yield of combined isomers. [d] dr ratio determined by NMR. [e] Pd/C, H_2, MeOH, rt.

(22) The mechanistic basis of stereoselectivity is under investigation. See the Supporting Information for preliminary studies.

(23) See the Supporting Information for the preparation of substrates. The relative stereochemistries were determined by NOE studies of both *cis* and *trans* isomers after removal of the Cbz group.

(24) The stereochemistry of **4f′-*cis*** was confirmed by X-ray analysis.

Scheme 3. Substrate Scope in the Diastereoselective Intramolecular Aza-Michael Addition[23]



The all-carbon chain substrate **3g** demonstrated excellent reactivity and stereochemical control comparable to the morpholine substrates. The lower homologue substrate (**3h**) showed great conversion, but only moderate diastereoselectivity was observed. Finally, the higher homologue substrates (**3i**, **3j**) did not provide the cyclized products.

Additional nitrogen-containing bicyclic heterocycles were also synthesized as a step toward sp^3-enriched compound libraries.[25] The resulting products of the aza-Michael reaction are excellent substrates in efforts to synthesize skeletally and stereochemically diverse compounds for small-molecule screening. After Cbz removal, morpholine derivative **2a′** was treated with polarized olefins, yielding a bicyclic product (Scheme 4).[26] Both **2a′-*cis*** and **2a′-*trans*** reacted with nitroethene to give high yields and diastereoselectivities. When β-nitro styrene was used,

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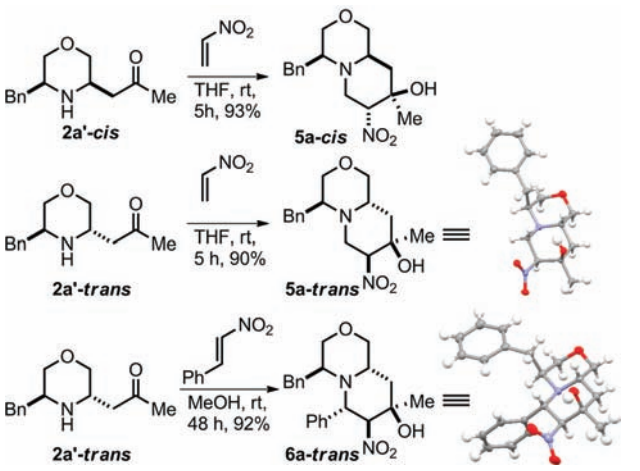
Scheme 4. Nitrogen-Containing Bicyclic Heterocycles Syntheses



2a′-*cis* was unreactive, even under forcing conditions. This is likely due to the *syn*-pentane-type repulsion between the benzyl and phenyl. However, **2a′-*trans*** gave the product **6a-*trans*** in high yield and diastereoselectivity. The X-ray structures of **5a-*trans*** and **6a-*trans*** confirmed their relative stereochemistries.

In summary, complementary outcomes of diastereoselective intramolecular aza-Michael reactions are reported. A variety of 3,5-disubstituted nitrogen-containing heterocycles were prepared with good to excellent yields in three synthetic transformations. Both *cis* and *trans* isomers were obtained with excellent diastereoselectivities by using $(MeCN)_2PdCl_2$ and TfOH. Further investigation of the mechanisms accounting for the opposing diastereoselectivity resulting from these catalysts is underway. This report emphasizes the effectiveness and efficiency of achiral catalysts in controlling diastereoselectivity.

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Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.