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Catalytic Enantioselective *tert*-Aminocyclization by Asymmetric Binary Acid Catalysis (ABC): Stereospecific 1,5-Hydrogen Transfer

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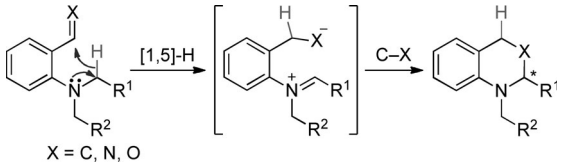
Initially disclosed in the 1970s and remaining largely ignored in the following decades,[1] the *tert*-amino effect and its related transformations have now been recognized in the pursuit of selective activation and functionalization of relatively inert C–H bonds, particularly sp^3 C–H bonds. In this regard, intramolecular *tert*-aminocyclization, a redox-neutral process involving a 1,*n*-hydride transfer, represents an intriguing cascade sp^3 C–H activation/C–X formation process for the synthesis of heterocyclic compounds.[2] Recently, both Lewis and Brønsted acids have been shown to promote this previous thermal process with greatly improved activity and synthetic applicability.[3] In light of its atom and redox economy as well as its significant synthetic potential, as in the asymmetric synthesis of PNU-286607,[4] the development of catalytic enantioselective *tert*-aminocyclization has been frequently attempted, with successes reported only recently. In 2009, Seidel and co-workers reported the first catalytic enantioselective *tert*-aminocyclization reaction using a chiral magnesium complex.[5] Chiral metal complexes such as cobalt[6] and gold complexes[7] as well as chiral organocatalysts such as diphenylprolinol[8] and phosphoric acids[9] were subsequently developed as chiral catalysts for this transformation. Despite those advances, the development of new asymmetric catalysts is still highly desirable for further improvements in activity, stereoselectivity, and applicability.

The mechanistic details of *tert*-aminocyclization remain obscure, particularly regarding the catalytic asymmetric processes for this appealing redox-neutral sp^3 C–H bond activation reaction. It is known that *tert*-aminocyclization involves a rate-limiting 1,5-H transfer and subsequent stereocenter-generating C–X bond formation (Scheme 1).[1,2] This mechanistic feature poses an intriguing challenge in controlling a likely stereoselective 1,5-H transfer as initially proved by Reinhoudt et al.[10] in the thermal cyclization of chiral tertiary amines and recently verified by Akiyama et al.[9] in chiral phosphoric acid catalyzed *tert*-aminocyclization. Regarding the enantioselective catalytic process, however, there is currently no experimental information about the proton transfer pathway nor its stereochemical features. It also remains unclear how a rate-limiting 1,5-H transfer dictates the subsequent stereocenter-generating C–X bond formation step. Elucidation of these mechanistic details would certainly facilitate the exploration of distinctive new designs in asymmetric catalysts.



Scheme 1. Activation of sp^3 C–H through 1,5-H transfer/ring closure process.

We have recently been developing chiral Brønsted acids, such as chiral monophosphoric acid, as dual ligands and acid catalysts for metal catalysis.[11] This binary catalytic system synergistically integrates chiral Brønsted acids and metal catalysts, leading to mutually enhanced acidity/electrophilicity and multiple sites for substrate binding due to their weak coordinating behavior. These features, together with combinatorial flexibility, inspired us to explore this binary acid strategy in the hitherto less developed asymmetric *tert*-aminocyclization reaction. Herein we present our initial efforts in this regard, which allowed us not only to identify a remarkably effective and selective binary acid catalyst, but to disclose interesting mechanistic features regarding 1,5-H transfer and the mode of stereocontrol.

We started with chiral phosphoric acid as the selected Brønsted acid ligand in the cyclization of **1a**. Previously, Akiyama and colleagues reported that the sole use of chiral phosphoric acid was successful in promoting the reaction of acyclic tertiary amines with good enantioselectivity at high temperature.[9] Unfortunately, the reaction with cyclic tertiary amines gave rather low enantioselectivity (e.g., $<10\%$ *ee* for **1a**). In our studies, it was found that chiral phosphoric acid alone could not catalyze the reactions of cyclic tertiary amine **1a** (Table 1, entry 1). The combination of chiral phosphoric acid **2a** with various Lewis acids was then examined (Table 1). To our delight, the combined use of Lewis acids and **2a** resulted in smooth reactions with activity similar to, or even better than, that with Lewis acid alone (e.g., Table 1, entries 5 versus 22) under ambient temperature. Among the many different Lewis acids screened,

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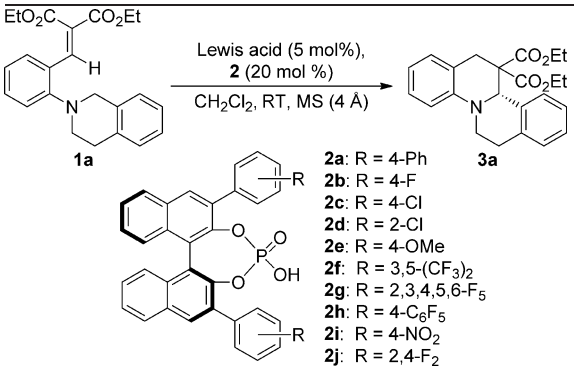
Table 1. Screening and optimization.



Entry[a]	Lewis Acid	Phosphoric Acid	t [h]	Conv. [%][b]	*ee* [%][c]
1[d]	–	**2a** or **2j**	15	trace	–
2	$Mg(OTf)_2$	**2a**	15	quant.	13
3	$Ni(OTf)_2$	**2a**	15	quant.	rac
4	$Cu(OTf)_2$	**2a**	15	quant.	12
5	$MgCl_2$	**2a**	15	quant.	43
6	$Zn(OTf)_2$	**2a**	15	quant.	23
7	$MgCl_2$	**2b**	15	83	56
8	$MgCl_2$	**2c**	15	quant.	16
9	$MgCl_2$	**2d**	15	90	70
10	$MgCl_2$	**2e**	15	85	64
11	$MgCl_2$	**2f**	15	quant.	21(*R*)
12	$MgCl_2$	**2g**	15	quant.	16
13	$MgCl_2$	**2h**	15	quant.	19(*R*)
14	$MgCl_2$	**2i**	15	91	13
15	$MgCl_2$	**2j**	15	quant. (95)[e]	93
16	$Mg(OTf)_2$	**2j**	15	98	87
17	$Mg(BF_4)_2$	**2j**	8	quant.	89
18	$Mg(BArF)_2$	**2j**	6	quant.	87
19	$Mg(SbF_6)_2$	**2j**	3	quant.	87
20	$MgCl_2$	**2j** (1:3)[f]	15	quant.	90
21	$MgCl_2$	**2j** (1:1)[f]	15	quant.	83
22	$MgCl_2$	–	15	quant.	–
23	$Mg(\mathbf{2j})_2$	–	18	99	rac

[a] Reaction conditions: **1a** (0.05 mmol), Lewis acid (0.0025 mmol, 5 mol%), phosphoric acid (0.01 mmol, 20 mol%), MS (4 Å, 15 mg), CH_2Cl_2 (0.5 mL) at ambient temperature under Ar. [b] Conversions were determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined by HPLC. [d] Without Lewis acid. [e] Isolated yield.

$MgCl_2$ was found to deliver an encouraging 43% *ee* (Table 1, entry 5). A survey of various phosphoric acids was next conducted in the presence of 5 mol% $MgCl_2$ (Table 1, entries 8–15). Biphenyl phosphoric acid **2j**, bearing 2,4-bis-fluorophenyl groups, turned out to be the best co-catalyst for this transformation, and the tetrahydroquinoline product **3a** was obtained in 95% isolated yield and 93% *ee* at ambient temperature in 15 h. To the best of our knowledge, this represents the best result for this type of substrate.

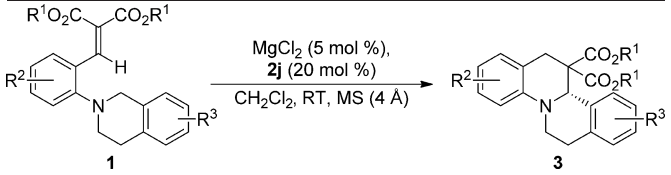
Magnesium salts with different anions were also examined (Table 1, entries 16–19), most of which gave similar chemical outcomes and enantioselectivity. Interestingly, although the reaction catalyzed by the magnesium salt of **2j** proceeded quite smoothly, it surprisingly afforded only racemic product (Table 1, entry 23). This observation highlights the critical role of free phosphoric acid and its synergistic combination with $MgCl_2$. Different molar ratios of $MgCl_2$/**2j** were also examined, and a 1:4 ratio is optimal in terms of enantioselectivity (Table 1, entries 20 and 21 versus 15). In our subsequent investigations, it was found that product enantiomeric excess value correlates linearly with that of **2j**, indicating that a high-order $MgCl_2$/**2j** complex is unlikely to be the real catalytically active species, and that an active 1:1 complex can be invoked (see the Supporting Information for the correlation diagram). Hence, the requirement of excess phosphoric acid beyond a 1:1 molar ratio for stereocontrol is most likely a physicochemical consequence for full coordination with $MgCl_2$ due to the low coordinating capability of phosphoric acid,[11a,12] thus eliminating any possible background reaction.

With the optimal catalyst system in hand, the substrate scope was next explored (Table 2). Various diester groups (methyl, ethyl, or benzyl) are well tolerated in the reactions, with excellent reactivity and enantioselectivity (Table 2, entries 1–3). Substrates with an electron-withdrawing group (chloro, bromo, or trifluoromethyl) *meta* or *para* to the nitrogen atom also gave the desired products with good isolated yields (>95%) and high enantioselectivity (92–94% *ee*) (Table 2, entries 4–7). However, the substrate bearing an electron-donating group (methoxy) *meta* to the nitrogen atom showed low activity (28%) but moderate enantioselectivity (66% *ee*; Table 2, entry 8). Prolonging the reaction time gives no significant improvement (108 h, 34% conversion, 68% *ee*). On the other hand, an electron-donating group on the tetrahydroisoquinoline moieties did not influence the reaction outcome significantly (Table 2, entries 9 and 10). Notably, catalyst loading can be decreased to 2.5 mol% ($MgCl_2$) while still maintaining good activity and enantioselectivity (Table 2, entries 4–6). The absolute configuration of **1b** was determined to be *S* ($[\alpha]^{20}_D = -81.0$ ($c = 1.0$, CH_2Cl_2)) by comparing its optical rotation with published data[7] ($[\alpha]^{26}_D = -83.1$ ($c = 0.5$, CH_2Cl_2)).

Other tertiary amines were also examined (Table 3). The use of $Mg(BF_4)_2$ was found to provide optimal activity and enantioselectivity. In all these cases, the reactions occurred smoothly under rather mild reaction conditions at ambient temperature to afford the desired products in quantitative yields with moderate to good enantioselectivity. Both cyclic and acyclic tertiary amines can be incorporated into the current protocol with good enantioselectivity. For example, the reactions of cyclic tertiary amines with five-, six-, or seven-membered rings gave 48–89% *ee* (Table 3, entries 1–4). Challenging substrates such as dibutylamino **3o** and diallylamino **3p** also worked very well to furnish 70 and 69% *ee*, respectively (Table 3, entries 5 and 6).

Mechanistic studies were then undertaken to elucidate the 1,5-H transfer pathway as well as the accompanying mode of stereocontrol. Firstly, deuterium-labeled substrates **1s** and **1t** were synthesized to probe the hydrogen transfer pathway. In the reaction of *rac*-**1s**, the ratio between H-transferred product **3s-H** and D-transferred product **3s-D** was found to be 3.6:1, catalyzed by the *rac*-**2j**/$MgCl_2$ combination after quantitative conversion, indicating a large pri-

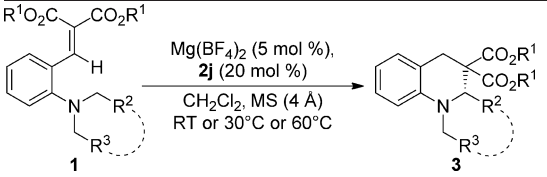
Table 2. Survey of substrate scope.



Entry[a]	Product	t [h]	Yield [%][b]	ee [%][c]
1	**3a**: R = Et	15	95	93
2	**3b**: R = Me	6	98	92
3	**3c**: R = Bn	18	98	92
4[d]	**3d**	11	>99	93
5[d]	**3e**	66	95	94
6[d]	**3f**	66	95	93
7	**3g**	15	97	92
8	**3h**	24	28	66
9	**3i**	15	>99	92
10	**3j**	64	99	85

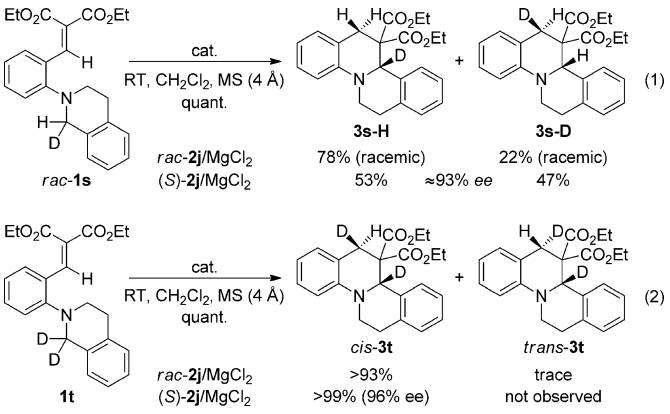
[a] Reaction conditions: **1a** (0.05 mmol), Lewis acid (0.0025 mmol, 5 mol%), phosphoric acid (0.01 mmol, 20 mol%), MS (4 Å, 15 mg), CH_2Cl_2 (0.5 mL) at ambient temperature under Ar. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC. [d] In the presence of $MgCl_2$ (2.5 mol%) and phosphoric acid (0.005 mmol, 10 mol%).

Table 3. Substrate scope of *tert*-aminocyclization.



Entry[a]	Product	t [h[	Yield [%][b]	ee [%][c]
1[d]	**3k**: R = Et	16	99	89
2[d]	**3l**: R = Me	21	98	88
3[e]	**3m**	30	99	81
4[e]	**3n**	16	95	48
5[f]	**3o**	10	99	70
6[f]	**3p**	18	95	69
7[e]	**3q**	21	95	74
8[f]	**3r**	20	99	86

[a] Reaction conditions: **1a** (0.05 mmol), Lewis acid (0.0025 mmol, 5 mol%), phosphoric acid (0.01 mmol, 20 mol%), MS (4 Å, 15 mg), CH_2Cl_2 (0.5 mL) under Ar. [b] Isolated yield. [c] Determined by HPLC. [d] In the presence of $MgCl_2$ (2.5 mol%) and phosphoric acid (0.005 mmol, 10 mol%). [e] At 60 °C with $ClCH_2CH_2Cl$ as solvent. [f] At 30 °C.



Scheme 2. The *tert*-aminocyclization of deuterated substrates **1s** and **1t**.

mary kinetic isotope effect ($k_H/k_D = 3.6$) in both cases (Scheme 2, [Eq. (1)]). That the rate-limiting step comprises 1,5-H transfer can thus be verified in the context of asymmetric catalysis.

1,5-Suprafacial hydrogen transfer is known to be a favorable process,[13] and in the *tert*-aminocyclization reaction this was experimentally proven by Reinhoudt and co-workers in the thermal cyclization of optically pure 2-vinyl-*N*,*N*-dialkylanilines (the tertiary amines).[10b,d] To track the pathway of hydrogen transfer in the catalytic asymmetric process, deuterated substrate **1t** was subjected to catalysis by (*S*)-**2j**/$MgCl_2$. The reaction afforded exclusively a single isomer, *cis*-**3t**, with 96% *ee* in quantitative yield (Scheme 2, [Eq. (2)]). Both the transferred deuterium and the bridge-

head deuterium atoms were found to be at the same face of **3t**,[14] and this 1,3-*cis* configuration is maintained in the reaction catalyzed by *rac*-**2j**/$MgCl_2$ (Scheme 2, [Eq. (2)]). In consistency with Reinhoudt's previous studies, the 1,3-*cis* configurations between the transferred hydrogen and bridgehead group supports a suprafacial 1,5-H transfer, and this transfer is *highly stereospecific* in the current process, as unequivocally proven by the observed high enantio- and diastereoselectivity (Scheme 2, [Eq. (2)]).

The labeling experiments also showed quite unexpected yet interesting results, revealing some hidden mechanistic features (Scheme 2, [Eq. (1)]). In subjecting *rac*-**1s** to catalysis by (*S*)-**2j**/$MgCl_2$, H-transferred product **3s-H** and D-transferred product **3s-D** were obtained in equal amounts (molar ratio 1:1), overriding the kinetically preferable hydrogen transfer, as is the case with the racemic **2j**/$MgCl_2$ combination.

DFT calculations were conducted to explore the mechanistic details. Indeed, suprafacial 1,5-H transfer is generally favored by 2.8 kcal mol^{-1} over antarafacial transfer for both thermal and $MgCl_2$-catalyzed processes (see the Supporting Information for details). Further DFT calculations on the $MgCl_2$-catalyzed process with a model compound revealed a major activation barrier for 1,5-H transfer (**TS1**, Figure 1) followed by a small conformational change in the resulting helical zwitterionic intermediate (**TS2**, Figure 1), leading to C–C formation without any detectable energy barrier. Consequently, C–C formation would occur without significant charge redistribution and structural equilibration, and thus the stereochemistry of the helical zwitterionic intermediate can be largely retained and transferred.

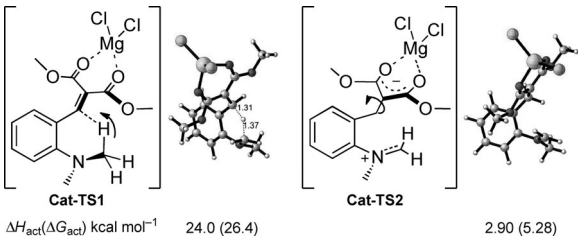
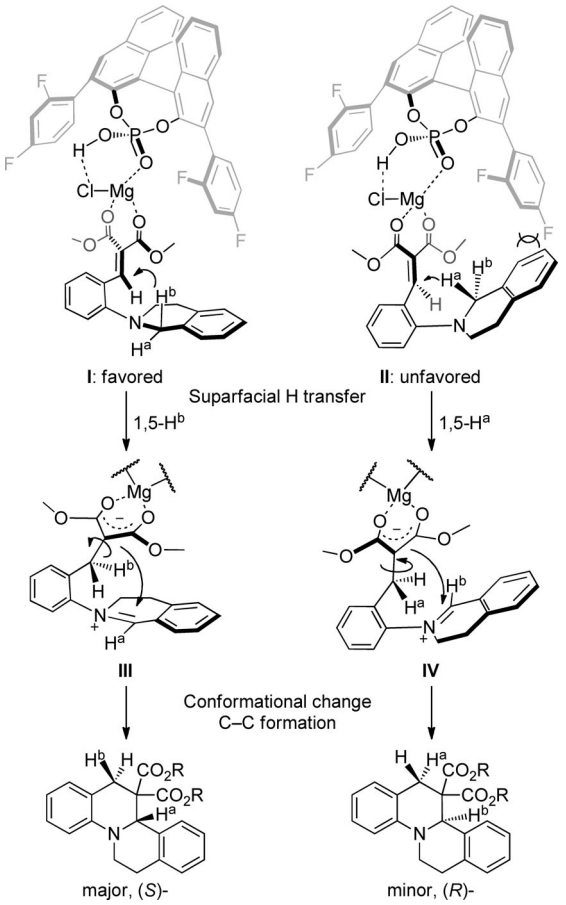


Figure 1. The transition states **TS1** and **TS2**, corresponding to 1,5-H transfer and conformational change, respectively, for $MgCl_2$-catalyzed *tert*-aminocyclization.

On the basis of DFT studies, plausible transition states were proposed to explain the experimental observations (Scheme 3). A 1:1 ratio of Mg^{2+}/**2j** is invoked to be the catalytically active species based on the linear correlation results (see the Supporting Information for details). Accordingly, upon complexation with Mg/**2j**, both H^a and H^b on the isoquinoline methylene carbon atom may participate in 1,5-H transfer, requiring two different helical conformations **I** and **II**, respectively, due to the suprafacial constraint. Of the two complexes, **I** is favored over **II** owing to its space tolerance (Scheme 3). This preferential activation can even override the H/D isotope effect, resulting in equal H and D



Scheme 3. Proposed transition states.

transfer with *rac*-**1s**, as shown in Scheme 2, [Eq. (1)]. The selective activation in complex **I** initiates 1,5-H^b transfer (**I**, Scheme 3), leading to the chiral helical zwitterionic intermediate III. After a small conformational change, the C–C bond would be form spontaneously with preserved stereochemistry.

In conclusion, we have developed a highly effective asymmetric binary acid catalyst MgX_2/**2j** for *tert*-aminocyclization reactions. The identified optimal catalytic system exhibits extremely high activity and good enantioselectivity for a broad range of substrates. Preliminary mechanistic studies indicated that the catalytic 1,5-H transfer proceeds stereospecifically in a suprafacial manner. The chiral binary acid complex selectively recognizes and activates one helical conformation, required for 1,5-suparafacial hydrogen transfer, explaining the observed stereoselectivity. Further investigations and detailed mechanistic studies to explore asymmetric redox-neutral sp^3 C–H bond functionalization with asymmetric binary acid catalysis are currently underway.

Experimental Section

General procedure for binary acid catalyzed *tert*-aminocyclization: $MgCl_2$ (0.24 mg, 5 mol %), catalyst **2j** (5.72 mg, 20 mol %), and molecular

sieves (4 Å, 15 mg) were added to a Schlenk-type flask under Ar. CH_2Cl_2 (0.25 mL) was then added, and the resulting mixture was stirred for 30 min. A solution of compound **1a** (0.05 mmol **1a** in 0.25 mL CH_2Cl_2) was added, and the resulting reaction mixture was stirred for 15 h at room temperature under Ar. The product was purified by silica gel column chromatography (EtOAc/PE 1:20 with 2% Et_3N) to give product **3a** as a colorless liquid.

Acknowledgements

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Keywords: asymmetric catalysis · C–H activation · hydrogen transfer · Lewis acid · phosphoric acid

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[12] The chiral phosphoric acid was washed extensively with concentrated HCl to remove any metal salt impurities. See previous discussions on this issue: M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911–3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826. The fact that different magnesium salts (some of which are soluble in organic solvents) perform similarly suggests that solubility is not a concern under the present conditions.

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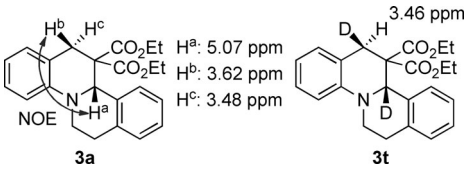
[14] The chemical shifts and configurations of H^a, H^b, and H^c in **3a** were assigned and determined based ^{1}H NMR and NOE analysis (see the Supporting Information for details). Accordingly, the configurations of deuterated products (e.g., *cis*-**3t**) can be assigned by comparison of the respective proton signal as well as in analogy to the determined absolute configurations of **3a**.



3a **3t**

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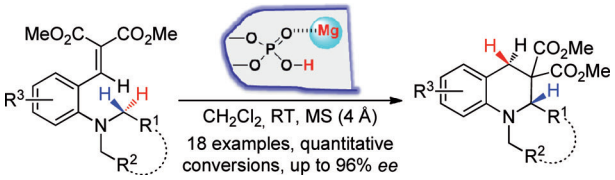
Asymmetric Catalysis



Selective H transfer by ABC: A new asymmetric binary acid catalyst was developed to promote 1,5-H transfer specifically and stereoselectively in *tert*-aminocyclization reactions with excellent activity, high enantioselectivity, and broad substrate scope. The H atom (in red) was proven to transfer through a stereospecific suprafacial pathway (see scheme).