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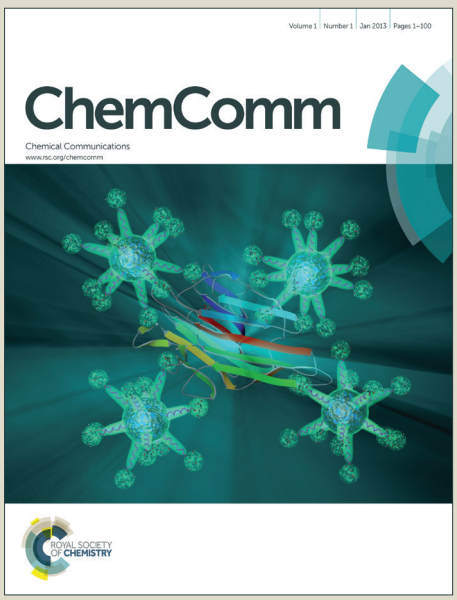

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ARTICLE TYPE

Catalytic Enantioselective Intramolecular Cyclization of N-Aryl Diazoamides Using Titanium-BINOLate Complex

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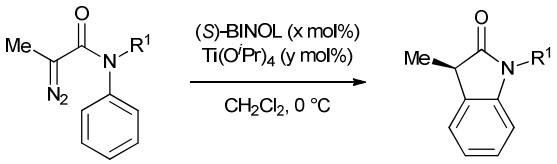
Described herein is the use of chiral titanium(IV)-BINOLate to formally implement catalytic asymmetric C(sp^2)–H insertion using N-aryl α-diazoamides. The reaction most likely proceeds via initial asymmetric protonation at the α-carbon of the substrate, followed by the intramolecular electrophilic aromatic substitution.

α-Diazocarbonyl compounds have found unlimited synthetic applications in asymmetric catalysis, especially in the field of late transition metal catalyzed transformations via metal-carbenes.[1] Among these developments, asymmetric X–H insertion (X = C, N, O, Si and S) has been one of the most intensive research areas.[2] In the literature, there are also examples in which achiral acid catalyzes X–H insertion of α-diazocarbonyl compounds when the atom X possesses a nucleophilic character.[1a,1b] Although these reactions are supposed to proceed by an acid catalyzed electrophilic activation of α-diazocarbonyl compounds followed by the nucleophilic substitution of the diazonium intermediate, their extension to asymmetric catalysis has been only sporadically reported.[3-7] We report herein titanium-BINOLate complex catalyzed enantioselective intramolecular cyclization of N-aryl diazoamides in which initial asymmetric protonation by chiral Lewis acid-assisted Brønsted acid seems to be operative. This is an example wherein a chiral acid catalyst facilitated a formal asymmetric C(sp^2)-H insertion.

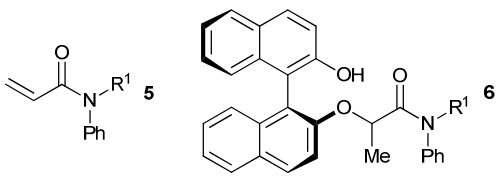
A clue to start this research was provided serendipitously during the course of our study using α-substituted α-diazocarbonyl compounds as nucleophile in acid catalysis.[8,9] When N-benzyl-N-phenyl diazoamide **1** was subjected to a reaction using titanium(IV)-BINOLate as catalyst, we observed the intramolecular cyclization of **1** to give the corresponding oxindole with modest enantioselectivity (Table 1, entry 1).[10-12] Optimization study revealed that the N-substituent of the diazoamide has a substantial effect on the reactivity and selectivity. Whereas the use of N-methyl diazoamide **2** led to a modest conversion after 20 h at 0 °C (entry 2), the reaction of N-diphenylmethyl diazoamide **3a** was found to be remarkably fast and gave oxindole **4a** in 77% yield within 2 h (entry 3). The enhanced reactivity can be explained by the facile cyclization due to the proximity of the reaction center imposed by the bulky diphenylmethyl group. In addition, the enantioselectivity could be remarkably improved to 96% ee. In these experiments, small amounts of the corresponding acrylamide **5** and the adduct of diazoamide and (*S*)-BINOL (**6**) were observed as byproducts. The high catalyst loading was found to be necessary as the reaction did not reach completion when the loading was reduced to half (entry 4). The 2:1 ratio of (*S*)-BINOL and Ti(O^{i}Pr)$_4$ was also important, as the use of catalyst composed of 40 mol% of each components remained incomplete even after 48 h (entry 5, 80% conversion). Interestingly, the reaction proceeded smoothly with 10 mol% Ti(O^{i}Pr)$_4$ when combined with 40 mol% (*S*)-BINOL (entry 6), underlying the importance of the amount of the phenolic proton source in the reaction (*vide infra*). Independent use of (*S*)-BINOL or Ti(O^{i}Pr)$_4$ did not catalyze the reaction at all (entries 7 and 8). The reactions were also carried out with Ti(O^{t}Bu)$_4$ and Ti(O^{n}Bu)$_4$, resulting only in the decrease of the enantioselectivity (entries 9 and 10).

Table 1 Optimization of the reaction conditions[a]



Entry	R^1	x	y	time (h)	% yield[b]	% ee[c]
1	Bn (**1**)	40	20	20	52	70
2	Me (**2**)	40	20	20	-[d]	-
3	CHPh$_2$ (**3a**)	40	20	2	77 (**4a**)	96
4	CHPh$_2$	20	10	48	-[d]	-
5	CHPh$_2$	40	40	48	-[d]	-
6	CHPh$_2$	40	10	8	77	72
7	CHPh$_2$	40	0	24	n.r.	-
8	CHPh$_2$	0	20	24	n.r.	-
9[e]	CHPh$_2$	40	20	2	72	91
10[f]	CHPh$_2$	40	20	8	67	80

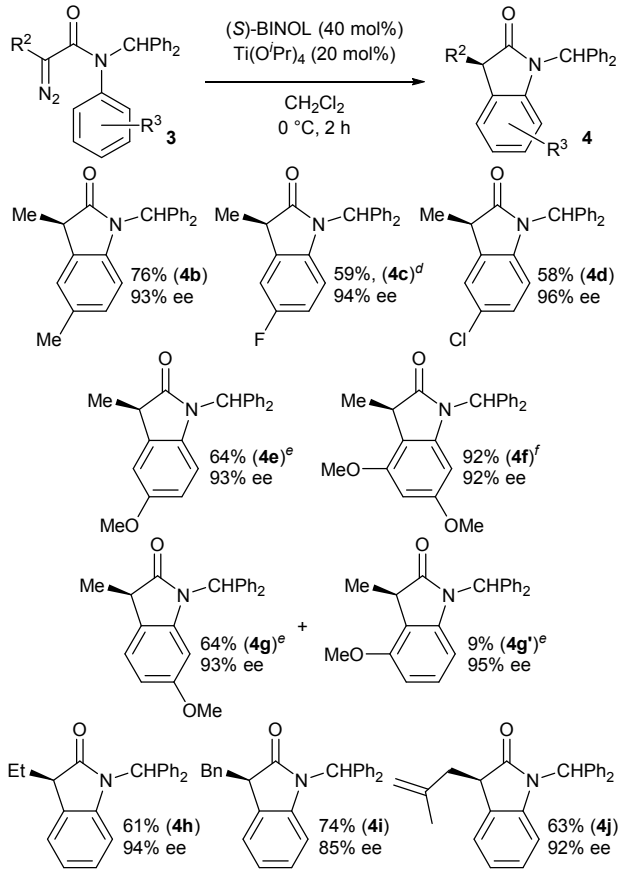
[a] Performed with N-phenyl diazoamide (0.25 mmol) in the presence of a 2:1 mixture of (*S*)-BINOL (0.10 mmol) and Ti(O^{i}Pr)$_4$ (0.05 mmol). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Not full conversion as determined by ESI-MS analysis. [e] Performed with Ti(O^{t}Bu)$_4$. [f] Performed with Ti(O^{n}Bu)$_4$.



With the optimized conditions in hand, we turned our attention to the substrate scope with regard to substituents of the N-aryl moiety and the alkyl group at the α-position (Table 2). The reactions with diazoamides having 4-methyl, 4-fluoro or 4-chloro

group gave the corresponding products **4b** to **4d**, respectively, in good yields with uniformly high enantioselectivities. In the case of N-(4-methoxyphenyl) diazoamide, the reaction was conducted at –20 °C to give **4e** with high enantioselectivity. Next, the tolerance of the substitution pattern on the aromatic ring was investigated. The reaction of N-(3,5-dimethoxyphenyl) diazoamide furnished oxindole **4f** in 92% yield with 92% ee. On the other hand, N-(2-methoxyphenyl) diazoamide was found to be an unsuitable substrate, giving a complex mixture after longer reaction time (data not shown). Subjection of N-(3-methoxyphenyl) diazoamide led to the preferential formation of sterically less encumbered **4g** in 64% with 93% ee, concomitant with a small amount of **4g'**. The focus was then moved to the tolerance of the α-alkyl group (R^2) of diazoamides. As typical examples, we carried out the reactions of ethyl, benzyl and methallyl substituted diazoamides to give rise to oxindoles **4h** to **4j**, respectively. Importantly, the alkene moiety remained intact in this titanium-BINOLate catalyzed reaction. The absolute configuration of the product was determined to be (*R*) by the X-ray crystallographic analysis of **4d** (see, SI).

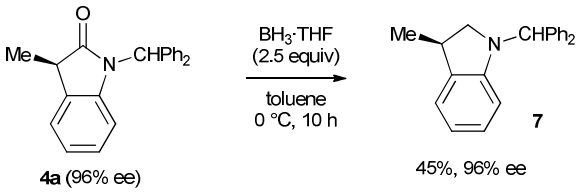
Table 2 Substrate scope[a-c]



[a] Performed with **3** (0.25 mmol) in the presence of a 2:1 mixture of (*S*)-BINOL (0.10 mmol) and $Ti(O^iPr)_4$ (0.05 mmol). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 6 h. [e] –20 °C, 2 h. [f] –30 °C, 8 h.

We then performed the borane reduction of **4a** as a synthetic application (Scheme 1). Although the concomitant formation of the corresponding indole became a substantial problem attenuating the reaction yield, 3-methylindoline **7** could be obtained in 45% yield without deterioration of the enantioselectivity.

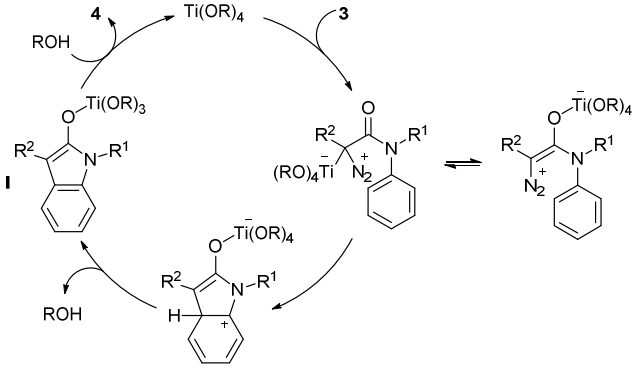
Scheme 1 Reduction of the chiral oxindole



To shed light on the reaction mechanism, an NMR experiment of the catalyst solution was conducted, while being aware of the complexity of the titanium-BINOLate in solution.[13] The NMR spectra in $CDCl_3$ showed apparent peaks of free (*S*)-BINOL, which implies the incomplete ligand exchange of (*S*)-BINOL and isopropanol (see Supplementary Information for details). Portionwise addition of diazoamide **3a** to this catalyst solution led to the gradual loss of free BINOL concomitant with the instantaneous formation of the product. After the disappearance of free BINOL, the substrate consumption became significantly retarded. This observation matches with the result of the reaction optimization (Table 1, entries 5 and 6), wherein the ratio and amount of BINOL had a drastic effect on the conversion.[14] It should be noted that the addition of the product oxindole **4a** to a fresh catalyst solution in $CDCl_3$ did not change the catalyst structure. In addition, an apparent product inhibition of the reaction was not observed.

One possible mechanistic scenario of this reaction is the intermediacy of titanium enolate **I** followed by asymmetric protonation by the remaining BINOL as shown in Figure 1.[15,16] However, we excluded this possibility due to the lack of observation of any titanium-enolate species throughout this NMR study, which should be formed even in the absence of a proton source.

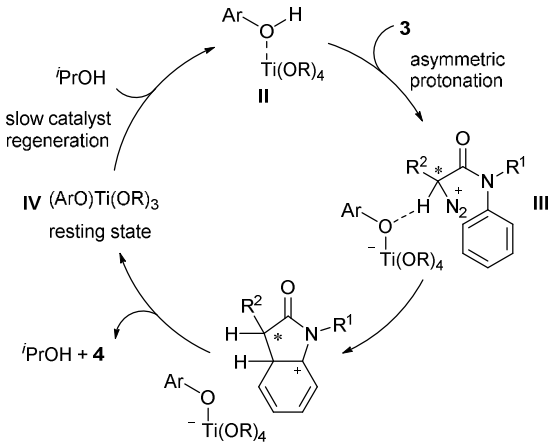
Figure 1 Reaction via a metal enolate. ROH = ^{i}PrOH and/or (*S*)-BINOL.



The other plausible mechanism consistent with this NMR experiment is the intervention of chiral Lewis acid-assisted Brønsted acid catalysis (Figure 2).[10,17,18] At the initial stage of the reaction, there is a substantial amount of (*S*)-BINOL which supplies its proton to the diazoamide via the formation of titanium Lewis acid-assisted Brønsted acid **II**, giving protonated diazonium species **III**. This unstable intermediate then undergoes electrophilic aromatic substitution to give the oxindole. The gradual decrease of the BINOL content in the solution and concurrent deceleration of the reaction can be rationalized by the formation of the catalyst resting state **IV**, most likely

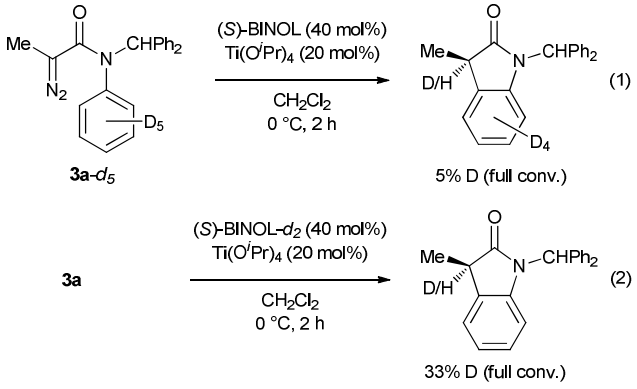
$(BINOLate)_2Ti$.[19] The active catalyst then regenerates through the slow ligand exchange with isopropanol.

Figure 2 Lewis acid-assisted chiral Brønsted acid catalysis. ROH = ^{i}PrOH and/or (*S*)-BINOL. ArOH = (*S*)-BINOL.



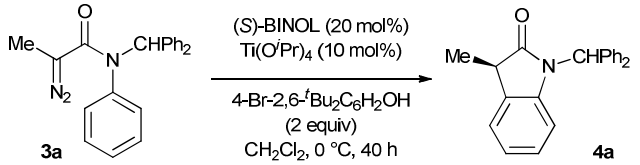
We then carried out a deuterium-labelling experiment with N-(D_5-phenyl) diazoamide **3a**-d_5 (98% *d*) (Scheme 2, eq. 1). To our surprise, only 5% of the α-hydrogen of the product was deuterated, suggesting the selective incorporation of proton derived from BINOL. Next, a reaction of non-dueterated **3a** using (*S*)-BINOL-d_2, wherein the phenolic proton was deuterated (>90% *d*), was implemented in anticipation of the selective deuteration (Scheme 2, eq. 2). However, even in this case, the deuteration level remained 33%. Furthermore, the reaction of fully dueterated system composed of **3a**-d_5 and (*S*)-BINOL-d_2 required 3 days for full conversion, highlighting the critical role of the protonation and/or proton transfer in the reaction rate.[20]

Scheme 2 Deuterium labelling experiments



While this puzzling observation could not be explained properly at this stage, the crucial role of the proton in the reaction rate and conversion is undeniable. This prompted us to examine an external proton source which is expected to facilitate the catalyst turnover and contribute to the reduction of the catalyst loading. This study revealed the effectiveness of 4-bromo-2,6-di-*tert*-butylphenol as additive, with which oxindole **4a** could be obtained in 68% yield and 90% ee within 40 h by using 20 mol% (*S*)-BINOL and 10 mol% $Ti(O^iPr)_4$ (Scheme 3). The acidity and the steric bulk of the phenol were both important to secure the reactivity and the selectivity.

Scheme 3 Use of an additional proton source to lower the catalyst loading



In conclusion, we have discovered that titanium-BINOLate complex facilitates enantioselective intramolecular cyclization of N-aryl diazoamides as a means to realize formal asymmetric $C(sp^2)$-H insertion. The titanium-BINOLate complex was assumed to act as a chiral Lewis acid-assisted Brønsted acid which protonates the substrate in an asymmetric manner.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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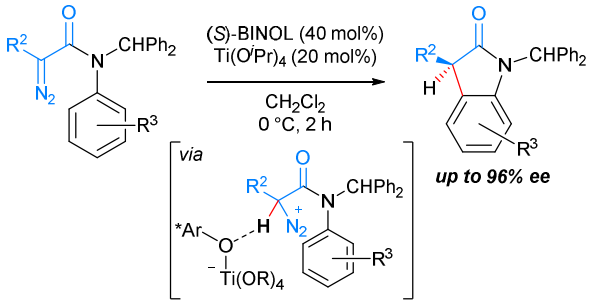
19 Addition of a base to a 2:1 mixture of BINOL and $Ti(O^iPr)_4$ is known to give $(BINOLate)_2Ti$, see ref 13a.

20 The level of the deuterium incorporation remained modest presumablely due to the gradual incorporation of the proton generated by the formation of acrylamide **5** and adventitious water.



Catalytic enantioselective intramolecular xyclization of N-aryl diazoamides was achieved by using titanium-BINOLate as chiral Lewis acid-assisted Brønsted acid.