Organic LETTERS

Letter

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Calcium-Catalyzed Asymmetric Synthesis of 3-Tetrasubstituted Oxindoles: Efficient Construction of Adjacent Quaternary and Tertiary Chiral Centers

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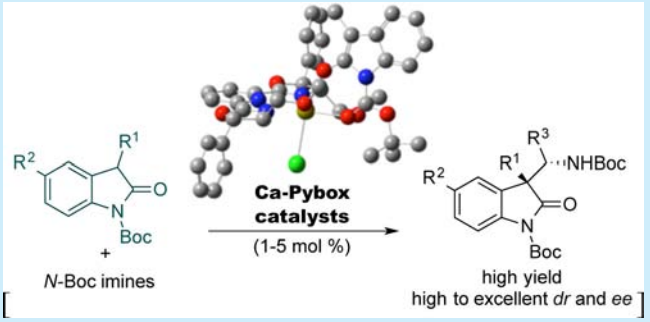
Supporting Information

ABSTRACT: Chiral Ca-catalyzed asymmetric addition reactions of 3-substituted oxindoles with *N*-Boc-imines afford 3-tetrasubstituted oxindole derivatives bearing adjacent quaternary and tertiary chiral centers, which are key structures for biological activities. Ubiquitous and nontoxic Ca catalysts (1−10 mol %) work well in this reaction, and high yields (up to 99%) and selectivities (up to >99% ee) of the products with wide substrate scope have been attained. The structures of the chiral Ca catalysts and intermediary Ca enolates are also discussed.



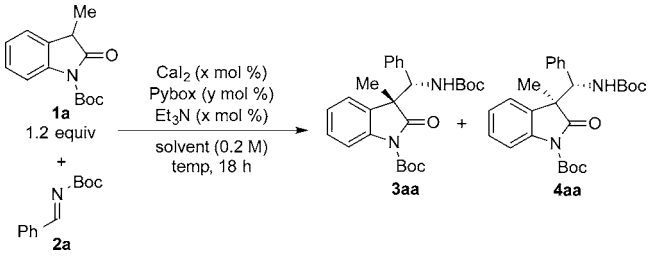
Oxindole derivatives are an interesting class of compounds for several biological activities, such as anticancer,[1] anti-HIV,[2] antimalarial,[3] antitubercular,[4] progesterone receptor agonist,[5] and MDM2 inhibitor,[6] etc.[7] For asymmetric synthesis of these compounds, construction of the quaternary chiral centers often observed in their structures is one of the most challenging tasks.[8] While the reactions of 3-substituted oxindoles with imines potentially provide an efficient method for making adjacent quaternary and tertiary chiral centers,[9] control of such stereogenic centers is known to be very difficult presumably because of steric congestion. Up to now, only four reports appear for this reaction, and yields, selectivities, catalyst efficiency, and/or substrate generality are not satisfactory.[10] In 2008, Chen and co-workers reported the first example of the reaction of 3-substituted oxindoles with *N*-Boc-imines using bifunctional thiourea−tertiary amine organocatalysts, and high enantioselectivities (up to 95% ee) were obtained for several 3-substituted oxindoles with aromatic and heteroaromatic *N*-Boc-imines.[10a] However, a racemic compound was obtained in a reaction with an aliphatic *N*-Boc-imine. In 2009, Maruoka and co-workers reported phosphonium salts as chiral phase-transfer catalysts and demonstrated the reactions of 3-aryloxindoles with aromatic *N*-Boc-imines and good enantioselectivities (up to 88% ee) were obtained.[10b] Liu, Chen, and co-workers reported modified cinchona alkaloid-catalyzed reactions of *N*-unprotected 3-substituted oxindoles with aromatic *N*-Ts-imines, and good enantioselectivities (up to 89% ee) were obtained.[10c] Finally, in 2013, Zhang and Peng reported the reactions of *N*-unprotected 3-bromooxindoles with aromatic *N*-Ts-imines catalyzed by bifunctional thiourea derivatives, and high enantioselectivities (up to 99% ee) were obtained.[10d] In those four reports, while high yields and high selectivities were obtained in some cases, substrates were limited to aromatic and heteroaromatic imines, and no enantioselective reactions with aliphatic imines were reported. In addition, organocatalysts (nonmetal catalysts) are used in all of the previous examples, and relatively high loading amounts of catalysts (10 mol %) are used except for phosphonium salts (3 mol %). Here, we report the reactions of 3-substituted oxindoles with *N*-Boc-imines using chiral calcium catalysts. Not only aromatic imines but also aliphatic imines work well, and high yields and high diastereo- and enantioselectivities have been attained using 1−10 mol % loadings of the calcium catalysts with wide substrate scope.

Recently, we have been interested in calcium compounds as catalysts in organic transformations. Calcium is a ubiquitous element, nontoxic, and readily available.[11] Previously, we have investigated chiral calcium alkoxide-catalyzed asymmetric reactions,[12] such as asymmetric Michael reactions,[12a−e,h,i] asymmetric [3 + 2] cycloaddition reactions,[12a,b,i] and asymmetric protonation reactions.[12f] More recently, we have developed chiral calcium chloride[12h,i] and chiral calcium iodide (CaI_2)[13] for catalytic asymmetric transformations. We chose 3-methyl-substituted oxindole **1a** and *N*-Boc-imine **2a** as models, and several reaction conditions were examined. It was found that a combination of CaI_2 with Pybox **L** gave promising results. When CaI_2 and **L1** were used, the reaction proceeded smoothly to afford the desired product **3aa** in 85% yield with high diastereoselectivity and moderate enantioselectivity (Table 1, entry 1). Ligand screening showed that **L5** gave the best enantioselectivity (entries 2−5). With the optimized ligand **L5**, several solvents were screened. Slightly higher enantioselectivities were observed when diethyl ether (Et_2O) and dichloromethane (DCM) were employed (entries 6−8). By lowering the

Received: March 17, 2015
Published: April 7, 2015

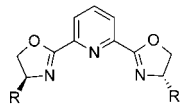
DOI: 10.1021/acs.orglett.5b00749
Org. Lett. 2015, 17, 2006−2009

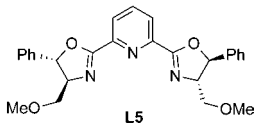
Table 1. Optimization of Reaction Conditions



entry	x	y	temp [°C]	Py-box	solvent	yield [%][a]	3aa:4aa[b]	ee [%][c]
1[d]	10	10	−40	**L1**	Tol	85	94:6	57
2[d]	10	10	−40	**L2**	Tol	85	94:6	21
3[d]	10	10	−40	**L3**	Tol	87	94:6	66
4[d]	10	10	−40	**L4**	Tol	86	95:5	21
5[d]	10	10	−40	**L5**	Tol	78	94:6	75
6[d]	10	10	−40	**L5**	Et_2O	83	95:5	78
7[d]	10	10	−40	**L5**	THF	80	95:5	31
8[d]	10	10	−40	**L5**	DCM	83	94:6	78
9[d]	10	10	−78	**L5**	DCM	88	94:6	93
10[d]	5	5	−78	**L5**	DCM	85	94:6	76
11[d]	5	7.5	−78	**L5**	DCM	85	93:7	99
12[e,f,g]	5	7.5	−78	**L5**	DCM	87	95:5	98
13[e,g,h]	3	4.5	−78	**L5**	DCM	91	95:5	97
14[e,g,h]	2	3	−78	**L5**	DCM	81	95:5	92
15[e,g,i,j]	1	1.5	−78	**L5**	DCM	97	94:6	98
16[f,g,k]	5	7.5	−78	**L5**	DCM	92	94:6	87
17[f,g,l]	5	7.5	−78	**L5**	DCM	89	94:6	14

[a]Isolated yield. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]Et_3N was added at −78 °C. [e]Et_3N was added at rt. [f]Slow addition of imine over 1 h; the reaction was further continued for 17 h. [g]**1a** (1.0 equiv), **2a** (1.5 equiv). [h]Slow addition of imine over 10 h; the reaction was continued for 8 h. [i]Slow addition of imine over 20 h; the reaction was continued for 22 h. [j]0.4 M. [k]$CaCl_2$ was used instead of CaI_2. [l]$Ca(O\text{-}i\text{-}Pr)_2$ was used instead of CaI_2 without Et_3N.

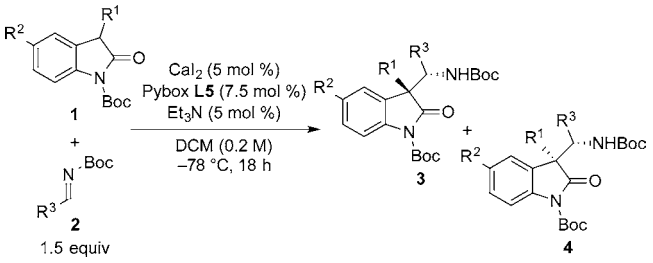




reaction temperature, the enantioselectivity was further improved to 93% ee (entry 9). To decrease the catalyst loading, several conditions were investigated (entries 10−15). When the ratio of CaI_2 to **L5** was 1:1.5, the desired product **3aa** was obtained in 87% yield with 95:5 dr and 98% ee (entry 12). Further decreasing the catalyst loading showed promising results (entries 13−15). Finally, the reaction proceeded smoothly to afford the desired adduct in 97% yield with high diastereoselectivity (**3aa**/**4aa** = 94/6), and the enantioselectivity of **3aa** was 97% using 1 mol % of the catalyst (entry 15). On the other hand, while the enantioselectivity decreased slightly using $CaCl_2$ instead of CaI_2 (entry 16), a significant drop in the enantioselectivity was observed when calcium isopropoxide ($Ca(O\text{-}i\text{-}Pr)_2$) was used as a calcium source (entry 17).

Next, we investigated the substrate scope of this asymmetric reaction (Table 2). When we applied tolyl imines **2b−d**, high yields, high diastereoselectivities, and excellent enantioselectivities were observed in all cases (entries 2−4). In the reactions

Table 2. Substrate Scope[a]



entry	R^1	R^2	R^3	yield[b] (%)	3:4[c]	ee[d] (%)
1	Me (**1a**)	H	Ph (**2a**)	87 (**3aa**)	95:5	98
2	Me (**1a**)	H	*o*-MeC_6H_4 (**2b**)	93 (**3ab**)	97:3	97
3[e]	Me (**1a**)	H	*m*-MeC_6H_4 (**2c**)	80 (**3ac**)	95:5	97
4[f]	Me (**1a**)	H	*p*-MeC_6H_4 (**2d**)	95 (**3ad**)	96:4	95
5	Me (**1a**)	H	*m*-$CF_3C_6H_4$ (**2e**)	93 (**3ae**)	96:4	97
6	Me (**1a**)	H	*p*-OMe C_6H_4 (**2f**)	91 (**3af**)	94:6	95
7	Me (**1a**)	H	*p*-ClC_6H_4 (**2g**)	92 (**3ag**)	97:3	96
8	Me (**1a**)	H	2-furyl (**2h**)	89 (**3ah**)	97:3	96
9	Me (**1a**)	H	2-thienyl (**2i**)	91 (**3ai**)	98:2	98
10	Me (**1a**)	H	2-naphthyl (**2j**)	84 (**3aj**)	97:3	97
11[f,g]	Me (**1a**)	H	Et (**2k**)	96 (**3ak**)	97:3	90
12[f,g,h,i]	Me (**1a**)	H	*n*-C_5H_{11} (**2l**)	95 (**3al**)	93:7	72
13[e,h,i]	Me (**1a**)	H	*i*-Bu (**2m**)	99 (**3am**)	94:6	84
14[e]	Bn (**1b**)	H	Ph (**2a**)	81 (**3ba**)	94:6	95
15[e]	Bn (**1b**)	H	2-thienyl (**2i**)	84 (**3bi**)	96:4	98
16	*n*-Pr (**1c**)	H	Ph (**2a**)	83 (**3ca**)	94:6	98
17	*n*-Pr (**1c**)	H	Et (**2k**)	43 (**3ck**)	97:3	72
18[e,h,i]	*n*-Pr (**1c**)	H	*i*-Bu (**2m**)	93 (**3cm**)	97:3	74
19	*i*-Pr (**1d**)	H	Ph (**2a**)	80 (**3da**)	95:5	>99
20[e,h,i]	*i*-Pr (**1d**)	H	*i*-Bu (**2m**)	77 (**3dm**)	95:5	73
21	**1e**[j]	H	Ph (**2a**)	80 (**3ea**)	95:5	93
22[f]	**1e**[j]	H	*p*-MeC_6H_4 (**2d**)	82 (**3ed**)	94:6	95
23[f]	**1e**[j]	H	*p*-ClC_6H_4 (**2g**)	88 (**3eg**)	96:4	97
24[e]	**1e**[j]	H	2-furyl (**2h**)	93 (**3eh**)	96:4	91
25	**1f**[k]	Me	Ph (**2a**)	93 (**3fa**)	94:6	95
26[e]	**1g**[l]	F	Ph (**2a**)	82 (**3ga**)	94:6	93

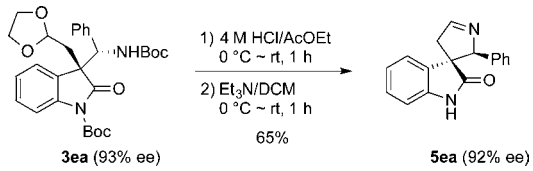
[a]**2** was added over 1 h unless otherwise noted. [b]Isolated yield. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]Slow addition of imine over 10 h; the reaction was further continued for 8 h. [f]Slow addition of imine over 5 h; the reaction was further continued for 13 h. [g]Imine (3 equiv) was used. [h]10 mol % of the catalyst was used. [i]Pybox **L3** was used. [j]**1e**: $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = H. [k]**1f**: $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = Me. [l]**1g**: $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = F.

with imines **2e**, **2f**, and **2g**, bearing electron-withdrawing and electron-donating substituents at the benzene rings, the reactions also proceeded smoothly to afford the desired products **3ae**, **3af**, and **3ag** in excellent yields with high diastereo- and enantioselectivities (entries 5−7). When heteroaromatic imines **2h** and **2i** were examined, excellent enantioselectivities were obtained (entries 8 and 9). The 2-naphthylaldehyde-derived imine **2j** also gave excellent enantioselectivity (entry 10). For aliphatic imines, imine **2k** derived from propionaldehyde reacted with oxindole **1a** to afford the desired product **3ak** in excellent yield with excellent diastereo- and enantioselectivities (entry 11). *n*-C_5H_{11} imine **2l** and *i*-Bu imine **2m** also reacted smoothly to provide the desired products **3al** and **3am**, respectively in excellent yields with good to high diastereo- and enantiose-

DOI: 10.1021/acs.orglett.5b00749
Org. Lett. 2015, 17, 2006−2009

lectivities using Pybox **L3** as the ligand (entries 12 and 13). It should be noted that aliphatic imines reacted smoothly to give the desired adducts in excellent yields with good to excellent diastereo- and enantioselectivies. In previous reports, as mentioned, there were no examples of enantioselective reactions using aliphatic imines.[10] The substrate scope of oxindoles **1** was also surveyed. 3-Benzyl-substituted oxindole **1b** reacted with imines **2a** and **2i** smoothly to afford the desired adducts in high yields with excellent diastereo- and enantioselectivities (entries 14 and 15). The absolute configuration was determined by comparing the optical rotation of **3bi** with that of the literature.[10a] 3-*n*-Propyl- and 3-isopropyl-substituted oxindoles **1c** and **1d** also reacted with imine **2a** smoothly, and almost perfect enantioselectivities were obtained (entries 16 and 19). Aliphatic imines **2k** and **2m** also worked well (entries 17, 18, and 20). We also examined the reactions of substituted oxindoles **1e**, **1f**, and **1g** (entries 21−26).[14] In all cases, the reactions proceeded smoothly to afford the desired adducts in high yields with excellent diastereo- and enantioselectivities. The adduct **3ea** was readily converted to spirooxindole derivative **5ea** in good yield without loss of any optical purity (Scheme 1).[15−17] Thus, we

Scheme 1. Transformation to Spirooxindole

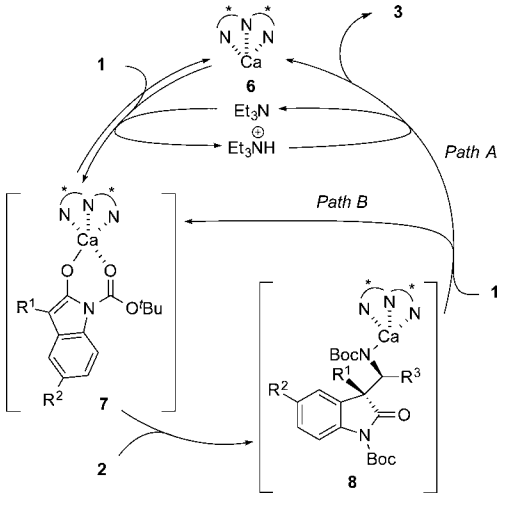


3ea (93% ee) **5ea** (92% ee)

have succeeded in providing oxindole derivatives that have adjacent quaternary and tertiary chiral centers in satisfactory yields and stereoselectivities with wide substrate scope.

An assumed catalytic cycle of this asymmetric reaction is shown in Scheme 2. CaI_2 and ligand **L5** may form a 1:1 complex (**6**) and a 1:2 complex in solution; that is supported by NMR experiments.[13,18] Chiral Ca catalyst **6** may work as a monomeric form because a linear correlation between ligand ee's and product ee's was observed.[18,19] Ca catalyst **6** activates oxindole **1** to form Ca enolate **7**, which was detected by ESI HRMS analysis.[18] One enantioface (the *Re* face) of **7** is effectively shielded by the chiral

Scheme 2. Assumed Catalytic Cycle[a]

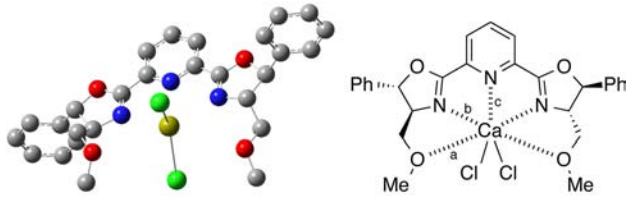


[a]Iodide ions are omitted for clarification.

ligand (vide infra), and **7** attacks imine **2**'s *Re* face smoothly to give intermediate **8**. There may be two possible ways to complete the catalytic cycle. In the first, the intermediate **8** is protonated by $Et_3NH^+I^-$ to give product **3** along with regeneration of the chiral Ca catalyst **6** (path A). In the second, the intermediate **8** deprotonates **1** to form the Ca enolate **7** (path B). Given the steric bulkiness of **1** and **8**, path A may be more likely; however, path B cannot be ruled out at this moment. It is noteworthy that the Ca catalysts, which have both mild Lewis acidity and Brønsted basicity,[11] may play a key role in obtaining high yields and stereoselectivities and also efficient catalyst turnover.

We further investigated stereochemical structures of the chiral Ca catalyst and the Ca enolate. While X-ray crystallographical analysis of $Ca(ClO_4)_2$−Pybox was conducted,[20] we carried out DFT calculation of $CaCl_2$−**L5** (Scheme 3).[21] The optimized

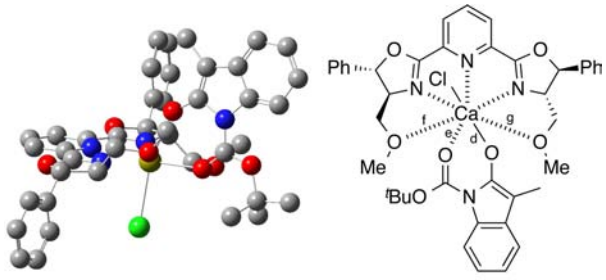
Scheme 3. Stereochemical Model of $CaCl_2$−L5



Blue N, Red O, Gray C, Green Cl, Yellow Ca;
a: 3.8 Å; b: 2.6 Å; c: 2.7 Å

structure has C_2-symmetry, and the three nitrogen atoms of **L5** coordinate to Ca. On the other hand, the length between Ca and O of the methoxy group of **L5** is 3.8 Å, suggesting weak coordination of O to Ca. We also investigated the structure of the Ca enolate (Scheme 4). The DFT calculation showed that the

Scheme 4. Stereochemical Model of Ca Enolate



d: 2.3 Å; e: 2.4 Å; f: 3.9 Å; g: 4.0 Å

three nitrogen atoms and the carbonyl oxygen of the Boc group coordinated to Ca. The length between Ca and O of the methoxy groups of **L5** is 3.9 and 4.0 Å, also suggesting weak interactions between O and Ca. The stereochemical model of the Ca enolate indicates that the plane of chiral ligand **L5** and the plane of the enolate are almost perpendicular and that the Re face of the enolate is efficiently shielded by the CH_2OMe arm of **L5**.

In conclusion, we have developed a new catalytic method for the synthesis of optically active 3-tetrasubstituted oxindoles using chiral Ca catalysts. Adjacent quaternary and tertiary chiral centers have been created efficiently by the Ca-catalyzed reactions of 3-substituted oxindoles with imines. High diastereo- and enantioselectivities have been realized with wide substrate scope. This is the first example of a chiral metal-catalyzed reaction of a 3-substituted oxindole with an imine. The

DOI: 10.1021/acs.orglett.5b00749
Org. Lett. 2015, 17, 2006−2009

ubiquitous and nontoxic Ca catalyst worked well, and even 1 mol % of the catalyst gave a high yield and high selectivities of the product. This reaction may provide an efficient approach to the synthesis of biologically important oxindoles, including spirooxindole derivatives. Further studies on this topic are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental section and copies of NMR spectra. 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.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, Japan Science Technology Agency (JST). We thank Mr. K. Takasugi (The University of Tokyo and JEOL Ltd.) for helpful discussions about NMR experiments.

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DOI: 10.1021/acs.orglett.5b00749
Org. Lett. 2015, 17, 2006−2009