2-Aminobenzimidazole Organocatalyzed Asymmetric Amination of Cyclic 1,3-Dicarbonyl Compounds

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Dedication – Dedicated to the memory of Prof. Carlos F. Barbas III.

Abstract: The use of a *trans*-cyclohexanediamine-benzimidazole derivative as hydrogen bond catalyst for the electrophilic amination of cyclic 1,3-dicarbonyl compounds is here presented. High yields and enantioselectivities varying form moderate to excellent are generally obtained using smooth reaction conditions and as low as 1 mol% of catalyst loading.

Key words: Organocatalysis, Electrophilic Amination, Asymmetric Catalysis, Dicarbonyl Compounds, Benzimidazole

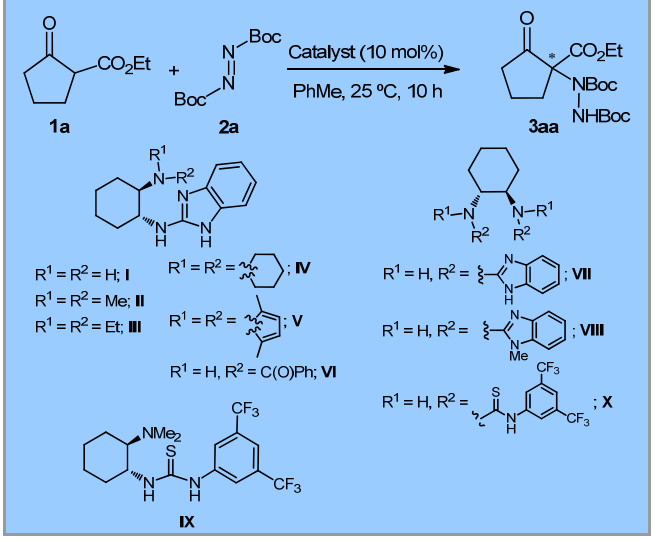
The construction of chiral quaternary stereocenters bearing an amine moiety represents an important reaction in synthetic organic chemistry due to the enormous amount of compounds possessing such structure in nature, most of them having biological and pharmaceutical activity.[1] In this sense, a wide variety of methods have been developed to gain access to these motifs. Among them, the asymmetric electrophilic amination of prochiral carbonyl compounds employing diazocarboxylates as nitrogen source is a simple and straightforward method since those latter reagents are bench-stable and readily available.[2]

Particularly interesting is the catalytic asymmetric α-amination of prochiral 1,3-dicarbonyl compounds, since the highly functionalized resulting structures can be further transformed and elaborated.[1-3] In this regard, several strategies have been developed in the last decades to successfully accomplish this transformation.[3] Thus, since the pioneer work of Jørgensen and coworkers using a copper(II)-box catalytic system,[4] different methods not only metal-catalyzed[5] but also employing organocatalysts[6-8] have been reported.

In the last years, our research group has been interested in the use of *trans*-cyclohexanediamine-benzimidazole derivatives as hydrogen bonding organocatalysts in different organic transformations.[9] Therefore, we decided to explore the performance of these catalysts in the electrophilic amination of 1,3-dicarbonyl compounds. The results of this study are herein disclosed.

First, the search for the appropriate catalyst to carry out this reaction was tackled using ethyl 2-oxocyclopentanecarboxylate (**1a**) and di-*tert*-butylazodicarboxilate (**2a**) as model substrates (Table 1). Thus, different *trans*-cyclohexanediamine-benzimidazole derivatives **I-VIII** were tested (Table 1, entries 1-8). The more basic catalysts **I-IV** afforded the corresponding amination product **3aa** in high conversions and enantioselectivities (Table 1, entries 1-4), reaching up to 90% *ee* in the case of dimethylamino derivative **II** (Table 1, entry 2). The presence of less basic nitrogen in catalysts, as is the case of **V** and **VI**, resulted in a dramatically drop of enantioselection (Table 1, entries 5 and 6). Next, bis(2-aminobenzoimidazole) derivatives **VII** and **VIII** were also evaluated, but lower results were observed in both conversion and enantioselectivity (Table 1, entries 7 and 8). Finally, for the sake of comparison, Takemoto's thiourea catalyst **IX** and the bisthiourea **X** were also evaluated but moderate conversion and enantioselectivity and low conversion was observed, respectively (Table 1, entries 9 and 10)

Table 1 Catalyst screening[a]



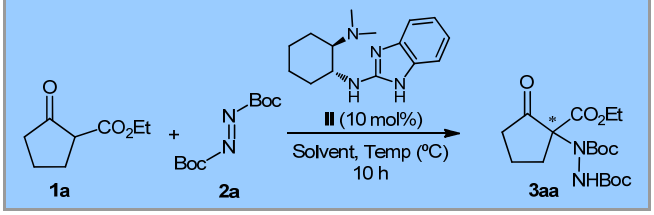
Entry	Catalyst	Conv (%)[b]	*ee* (%)[c]
1	**I**	>95	68
2	**II**	>95	90
3	**III**	>95	75
4	**IV**	>95	85
5	**V**	90	10
6	**VI**	80	*rac*
7	**VII**	90	50
8	**VIII**	15	*rac*
9	**IX**	70	65
10	**X**	<15	n.d.

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (10 mol%) in PhMe (1 mL).
[b] Determined by ^{1}H NMR analysis from the reaction crude.

[c] Determined by chiral HPLC (Daicel Chiralpak IA, see supporting information for details).

Once the organocatalyst screening revealed that benzimidazole **II** provided the best results, further optimization of reaction conditions was performed (Table 2). Firstly, different solvents were tested (Table 2, entries 1-7) obtaining the best results in terms of both conversion and enantioselectivity when toluene, diethyl ether and hexane were employed (Table 2, entries 1, 3 and 6). With these solvents the temperature influence was evaluated. Thus, at 0 ºC, the same results were observed (Table 2, entries 8-10) and lowering the temperature at -20 ºC resulted in lower conversions remaining the enantioselectivity the same. At this point, and since the influence of the temperature was negligible, we decided to continue the optimization at room temperature and using diethyl ether as solvent for solubility reasons. In order to avoid waste production we carry out the reaction using 1.05 eq. of **2a** and the same results were observed (Table 2, entry 11). Next, the effect of concentration of **1a** was studied, and exactly the same results were obtained using 0.2 and 0.05M reaction solutions (Table 2, entries 12 and 13), choosing the latter as optimal concentration. Finally, we tried to reduce the amount of catalyst and we were pleased to observe that not only 5 mol% (Table 2, entry 14), but also as low as 1 mol% of catalyst loading was enough to effectively promote the reaction with full conversion and excellent enantioselectivity (Table 2, entry 15).

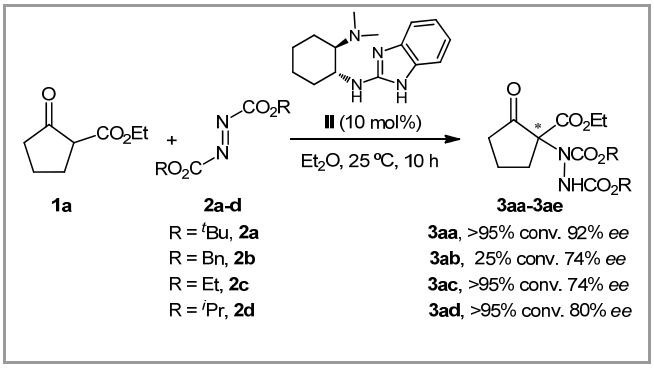
Table 2 Optimization of reaction parameters[a]



Entry	Solvent	Temp (ºC)	Conv. (%)[b]	*ee* (%)[c]
1	PhMe	25	>95	90
2	CH_2Cl_2	25	45	90
3	Et_2O	25	>95	92
4	THF	25	90	86
5	TBME	25	95	87
6	Hexane	25	>95	92
7	MeOH	25	90	52
8	PhMe	0	>95	90
9	Et_2O	0	>95	92
10	Hexane	0	95	92
11[d]	Et_2O	25	>95	92
12[e,d]	Et_2O	25	>95	92
13[f,d]	Et_2O	25	>95	92
14[g,d,e]	Et_2O	25	>95	92
15[h,d,e]	Et_2O	25	>95	92

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **II** (10 mol%) in 1.0 mL of solvent.
[b] Determined by ^{1}H NMR analysis from the reaction crude.
[c] Determined by chiral HPLC (Daicel Chiralpak IA, see supporting information for details).
[d] 0.105 mmol (1.05 eq.) of **2a** were used.
[e] 0.5 mL of Et_2O ([**1a**] = 0.2 M) was used.
[f] 2 mL of Et_2O ([**1a**] = 0.05 M) was used.
[g] 5 mol% of **II**, 0.5 mL of Et_2O.
[h] 1 mol% of **II**, 0.5 mL of Et_2O.

Then, with the optimal reaction conditions in hands (Table 2, entry 15), we decided to study the influence of diazocarboxylate structure (Scheme 1). Thus, *β*-keto ester **1a** was allowed to react with other different alkyl diazocarboxylates **2b-2d** but in all the cases the results turned out to be worse than in the case of **2a**.

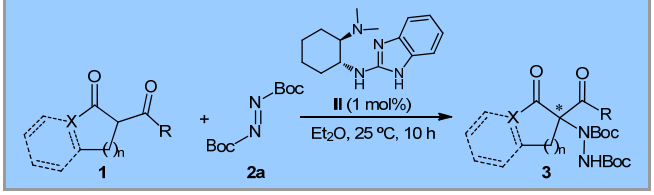


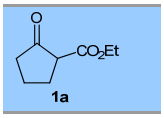
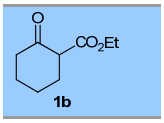
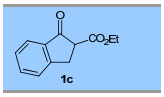
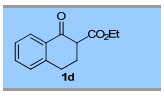
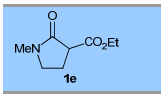
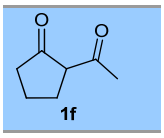
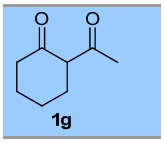
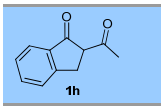
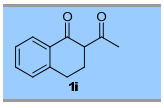
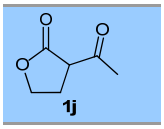
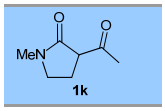
Scheme 1 Study of different diazocarboxylates

With all the reaction parameters optimized we next explored the subtrate scope (Table 3).[10] First, cyclic *β*-keto esters were examined. As previously commented **1a** yielded the desired product in high yields and with 92% *ee* (Table 3, entry 1). Surprisingly, when the six membered analogue was submitted to the optimal reaction conditions it failed completely, even though when higher catalyst loadings were assayed (Table 3, entry 2). The use of benzocondensed substrate **1c** rendered the amination product **3ca** in high yield and moderate enantioselectivity (Table 3, entry 3). In contrast, high optical purity along with high yield was obtained with keto ester **1d** (Table 3, entry 4). Cyclic *β*-amido ester was also examined but disappointingly low enantioselectivity was obtained despite several reaction conditions tested (Table 3, entry 5).

Next, the more reactive cyclic 1,3-diketones were taken into account. The five member ring diketone **1f** was firstly tested obtaining good yield and moderate enantioselectivity (Table 3, entry 6). In this case, the yield was slightly increased by using 5 mol% catalyst loading. As already observed in the case of keto esters, the six membered 1,3-diketone **1g** afforded low conversions at the best regardless the reaction conditions tested (Table 3, entry 7). The corresponding benzocondensed analogues **1h** and **1i** were also evaluated and in both cases high yields although with moderate enantioselectivities for the corresponding amination products were achieved (Table 3, entry 7). In both cases a slight increase of the optical purity was observed by lowering the temperature. Finally, compounds **1j** and **1k** gave rise to the corresponding amination products, **3ja** and **3ka** respectively, in good yields but with poor *ee*'s.

Table 3 Substrate scope[a]



Entry	1	3	Yield (%)	*ee* (%)
1		**3aa**	99	92
2		**3ba**	<10	n.d.
3		**3ca**	97	45
4		**3da**	98	88
5		**3ea**	87	20
6		**3fa**	75 (82)[d]	50
7		**3ga**	<10	n.d.
8		**3ha**	88 (70)[e]	27 (35)[e]
9		**3ia**	70 (68)[f]	48 (54)[f]
10		**3ja**	66	26
11		**3ka**	89	25

[a] Unless otherwise stated, the reaction conditions were: **1a** (0.20 mmol), **2a** (0.21 mmol), **II** (1 mol%) in Et_2O (1 mL), 25 ºC.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC (see supporting information for details).
[d] The reaction was carried out using 5 mol% of **II**.
[e] The reaction was carried out at –20 ºC.
[f] The reaction was carried out at –50 ºC.

It is important to mention that different linear *β*-keto ester and 1,3-diketones were also evaluated but, despite several efforts, racemic mixtures were obtained in all the cases.

Regarding the reaction mechanism, and based on previous computational and experimental studies carried out in our research group employing identical catalyst for the asymmetric conjugate addition of 1,3-dicarbonyl compounds onto nitroalkenes,[9a] we have proposed the catalytic cycle depicted in Figure 1 in which benzimidazole **II** could act as a bifunctional organocatalyst. Thus, firstly **II** would act as a base forming the corresponding 1,3-dicarbonyl compound enolate, which would coordinate through hydrogen bonding to the catalyst, as depicted at intermediate **A**. Then, the protonated dimethylamino moiety could activate the diazocarboxylate and hence facilitating the enantioselective attack of the enolate (intermediate B), releasing the corresponding amination product and regenerating the organocatalyst **II**.

It is also worth to mention that the (*S*)-configured amination product seems to be obtained when (*R*,*R*)-**II** is employed. This assumption was taken from optical rotation comparison between product **3aa** and the values reported in literature.[11]

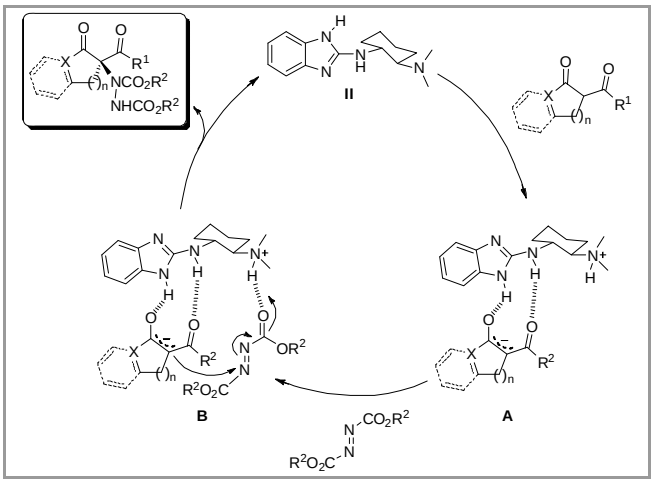


Figure 1 Proposed catalytic cycle

In conclusion, we have demonstrated that chiral *trans*-cyclohexanediamine-benzimidazole derivative **II** is a suitable and active organocatalyst for the asymmetric electrophilic amination of cyclic 1,3-dicarbonyl

compounds. The corresponding amination products are obtained in the majority of the cases with high yields and moderate to high enantioselectivities just using 1 mol% of catalyst loading. In addition, a bifunctional role of the catalyst is assumed due to a presumably dual hydrogen bond activation of both,the 1,3-dicarbonyl compound and the diazocarboxylate.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(10) **General procedure for the asymmetric amination of cyclic 1,3-dicarbonyl compounds:**
In a open air tube submerged in a thermostatized bath (25 ºC) the corresponding 1,3-dicarbonyl compound (0.2 mmol) was added to a solution of organocatalyst II (0.002 mmol, 1 mol%) in technical grade diethyl ether (1 mL). After 5 minutes, di-*tert*-butylazodicarboxilate **2a** (0.21 mmol, 1.05 eq.) was added in one portion and the reaction was then allow to react for 10 h. After this time, water (5 mL) and ethyl acetate were added, and then the aqueous layer was re-extracted twice (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Finally, the reaction crude was purified by flash chromatography using hexanes/ethyl acetate mixtures as eluent.
Physical and spectoscopical data given below are for compound **3da** and may be taken as representative. For further details see supporting information
Di-*tert*-butyl 1-(2-(ethoxycarbonyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate (3da)[8b]
Slightly yellow sticky oil; (88 mg, 98% yield, 91% *ee*). $[\alpha]_D^{28}$ = +23.3 (*c* = 2.0, $CHCl_3$).
^{1}H NMR (300 MHz): δ_H = 1.33 (br m, 21H), 2.67 (m, 1H), 2.95 (m, 2H), 3.44 (br m, 1H), 4.31 (*q*, J = 7.0 Hz, 2H), 6.23 (m, 1H), 7.25 (m, 2H), 7.46 (m, 1H), 7.95 (dd, *J* = 28.0, 7.2 Hz, 1H) ppm.
^{13}C NMR (75 MHz): δ_C = 14.1, 25.6, 27.7, 28.0, 31.1, 60.3, 61.9, 80.8, 82.7, 126.4, 127.7, 128.5, 131.7, 133.4, 154.4, 155.5, 169.5, 191.0 ppm.
MS (IE): m/z 348 [M^+ – Boc, 6.5%], 292 (47), 219 (100), 175 (86), 158 (30).

Chiral HPLC analysis: Chiralcel IA column, Hexane/^{i}PrOH 85:15, flow rate = 1 mL/min, λ = 254 nm, retention times: t_r = 8.0, **11.5** min.

(11) (*S*)-**3aa** $[\alpha]_D^{29}$ = +3.8 (c = 1, $CHCl_3$, 92% *ee*). Reported value in ref. 5b for (*R*)-enantiomer: $[\alpha]_D^{32}$ = –3.47 (c = 1.09, $CHCl_3$, 97% *ee*). See supporting information for further details.

Organocatalyzed Asymmetric Electrophilic Amination