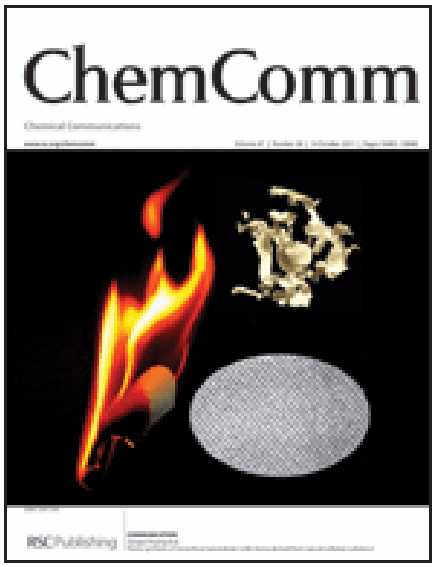

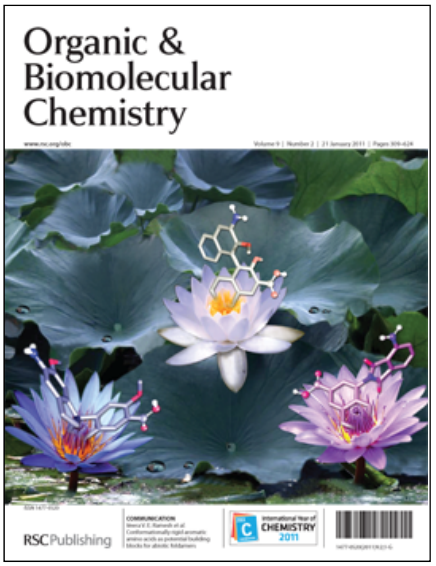

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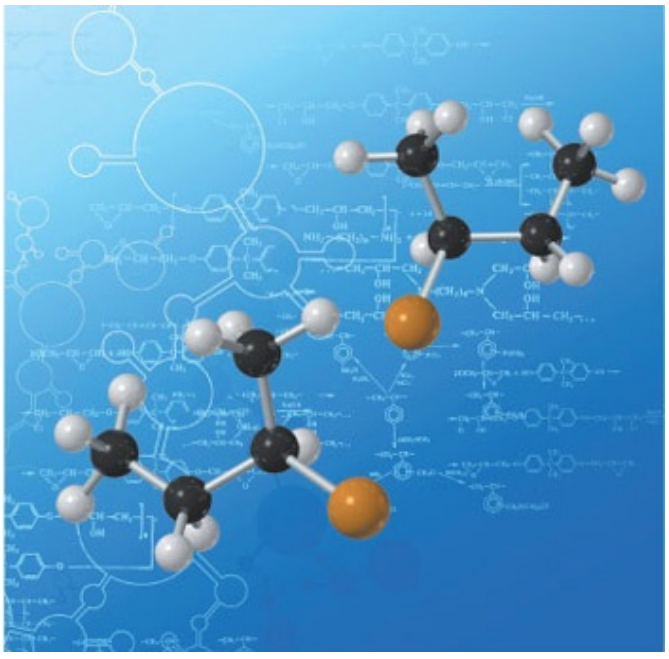

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COMMUNICATION

Direct amination of α-substituted nitroacetates using di-*tert*-butyl azodicarboxylate catalyzed by Hatakeyama's catalyst β-ICD†‡

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Received 18th October 2011, Accepted 13th December 2011
DOI: 10.1039/c2ob06746c

We report the first example of catalytic asymmetric direct amination of α-monosubstituted nitroacetates using di-*tert*-butyl azodicarboxylate. The simple and easily available Hatakeyama's catalyst β-ICD 11 was found to be a highly enantioselective catalyst for this reaction.

The catalytic asymmetric construction of tetrasubstituted carbon stereogenic centers is very important in asymmetric catalysis.[1] In this context, the use of a chiral Brønsted base for the deprotonative activation of carbon nucleophiles, with three disparate carbon substituents, to react with different electrophiles is a fruitful strategy.[1,2] A number of highly enantioselective transformations based on reactive nucleophiles such as α-substituted α-cyanoacetates, β-keto esters,[2a,b] and 3-prochiral oxindoles[2c] have been developed, allowing efficient synthesis of enantioenriched compounds with a tetrasubstituted chiral carbon stereocenter. However, the catalytic asymmetric functionalization of prochiral α-substituted nitroacetates has been much less studied judged by reaction type,[3] which was limited to Mannich[3a–f] and Michael addition[3g–n] reactions. Most recently, we reported the first example of catalytic asymmetric hydroxymethylation of α-substituted nitroacetates.[3o]

During the past decade, the direct C–N bond-forming reaction using azodicarboxylates has been established as a powerful strategy for the synthesis of nitrogen containing compounds.[4] In this context, Lewis acid catalyzed highly enantioselective amination of silyl enol ethers, β-ketoesters, pyruvic acid derivatives, enecarbamates and 3-prochiral oxindoles has been well developed.[5] The direct α-amination of aldehydes and ketones by enamine catalysis has also been intensively studied and became an efficient method for the enantioselective introduction of a nitrogen moiety to the α-position of the carbonyl group.[6] Brønsted base catalysis has also proven to be powerful in the direct asymmetric catalytic amination of active nucleophiles such as α-aryl substituted cyanoacetates, β-dicarbonyl compounds and 3-prochiral oxindoles.[7] Surprisingly, the direct amination of α-substituted nitroacetates using azodicarboxylates was largely unexplored. In 1976, Markovskii and Novikov reported that HgO could catalyze the reaction of nitromalonic ester with diethyl azodicarboxylate.[8] Since then, no further investigation was made into this amination reaction for more than 30 years.

During our efforts in the catalytic asymmetric construction of tetrasubstituted stereogenic carbon centers, we noticed that few methods allowed the construction of tetrasubstituted stereogenic centers with two amine substitutents.[9] In light of this, we re-examined this reaction and hoped to develop an enantioselective version, because the thus obtained compounds might be potentially useful, considering that aminals are a relatively common structural motif in bioactive compounds, including some commercial pharmaceuticals.[9,10] We began our condition optimization using nitroacetate **1a** to react with di-*tert*-butyl azodicarboxylate **2a** (DBAD). Some typical results are summarized in Table 1.

First, the evaluation of different catalysts was carried out by running the reaction at –40 °C in the presence of 10 mol% of chiral catalyst, with 1,1,2,2-tetrachloroethane (TTCE) as the solvent. Several typical Brønsted base catalysts **4–7** were first tried, and moderate yield and enantioselectivity were obtained (entries 1–4). Because the reaction proceeded slowly, we next tried the use of bifunctional Brønsted acid–base catalysts to improve the reactivity, with the acid moiety of the catalyst to activate the electrophile DBAD and the basic moiety to activate the nucleophile nitroacetate **1a**. While there was no obvious improvement in the reactivity and enantioselectivity when catalysts **8–10** were used (entries 5–7), the use of a simple and commercially available Hatakeyama's catalyst β-ICD **11**,[11] with a phenol group as the Brønsted acid moiety, afforded the desired product **3a** in 93% yield and 92% ee (entry 8). Further screening of different solvents revealed that CH_2Cl_2 was also a good reaction medium, and adduct **3a** could be obtained in excellent yield and slightly lower ee (entry 9). High ee was also obtained for product **3a** when reaction was carried out in toluene, THF, MeOBu^t, acetone or isopropyl acetate (entries 10–14), but the reactivities were not satisfactory. The structure of product **3a** was also confirmed by single-crystal X-ray diffraction (Fig. 1).[12]

On the basis of the above results, the examination of substrate scope was carried out using TTCE as the solvent, in the presence of 10 mol% of β-ICD **11**. The effect of the ester group of nitroacetate **1** was first checked. It was found that both isopropyl and ethyl

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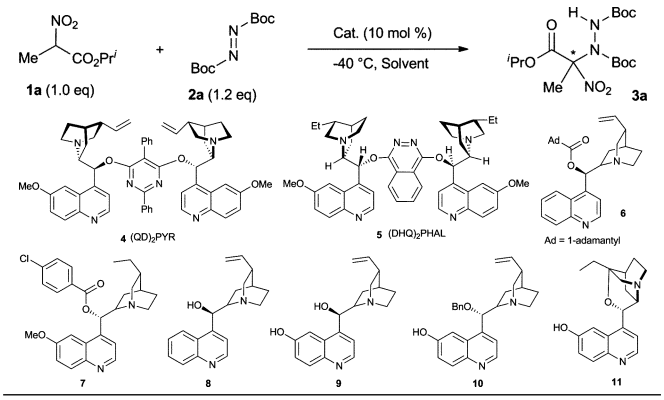
† This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available. CCDC reference number 833516. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06746c

Table 1 Catalyst screening and solvent effect



Entry[a]	Cat.	Solvent	Time (d)	Yield[b] (%)	ee[c] (%)
1	**4**	TTCE[d]	5	56	52[e]
2	**5**	TTCE	10	41	15[e]
3	**6**	TTCE	10	53	60
4	**7**	TTCE	10	24	24
5	**8**	TTCE	5	49	31
6	**9**	TTCE	5	32	68[e]
7	**10**	TTCE	5	34	60
8	**11**	TTCE	5	93	92
9	**11**	CH_2Cl_2	5	93	89
10	**11**	Toluene	5	90	84
11	**11**	THF	5	89	86
12	**11**	MeOBu^t	10	85	83
13	**11**	Acetone	10	85	85
14	**11**	$CH_3CO_2Pr^i$	10	89	89

[a] On a 0.25 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] TTCE ($Cl_2CHCHCl_2$). [e] Opposite enantiomer.

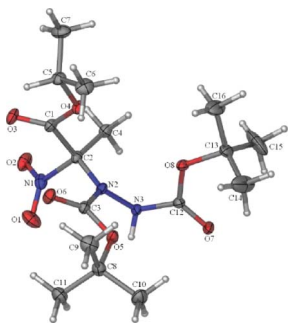
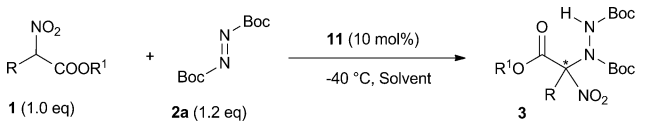


Fig. 1 X-ray structure of product **3a**.

ester **1a** and **1b** could afford the corresponding product **3a** and **3b** in excellent yield and enantioselectivity (entries 1–2, Table 2). Although *tert*-butyl α-methylnitroacetate **1c** could provide the desired product **3c** in excellent ee (entry 3), only 65% yield was obtained, possibly due to the steric effect resulting from the bulky *tert*-butyl ester group. In light of this, isopropyl or ethyl esters were used to react with DBAD in the following work. The substituents at the α-position of nitroacetates **1** obviously had an effect on the reactivity. The α-methylnitroacetate **1a** proved to be more reactive than other nitroacetates **1d–l** with larger α-substituents, and the corresponding amination adducts **3d–l** were obtained in lower yield than **3a** (entries 4–12). Although the α-substituents of nitroacetates **1** influenced the ee to some extent, the desired products **3d–l** were all obtained in high to excellent ee, with good to high yield (entries 4–12). We also tried several ethyl esters **1m–o**, which afforded the desired products **3m–o** in slightly higher enantioselectivity than the corresponding isopropyl esters **3j–l**, but the yield was lower (entries 13–15 *vs.* 10–12).

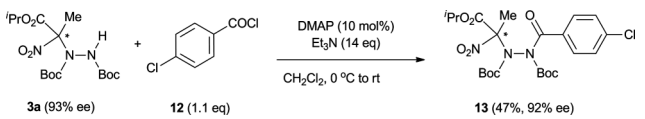
Table 2 Substrate scope of the amination of α-substituted nitroacetates



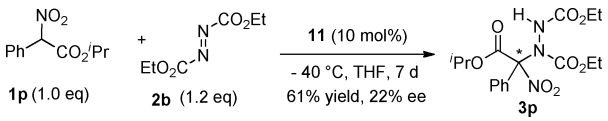
Entry[a]	R	3	Yield (%)[b]	$[\alpha]_D^{20}$	Ee[c] (%)
1	**1a**: R = Me, R^1 = *i*-Pr	**3a**	93	–94.2	92
2	**1b**: R = Me, R^1 = Et	**3b**	98	–84.8	91
3	**1c**: R = Me, R^1 = *t*-Bu	**3c**	65	–58.2	92
4[d]	**1d**: R = Et, R^1 = *i*-Pr	**3d**	87	–46.4	88
5	**1e**: R = *n*-Pr, R^1 = *i*-Pr	**3e**	60	–32.9	89
6	**1f**: R = *n*-Bu, R^1 = *i*-Pr	**3f**	60	–37.0	90
7[d]	**1g**: R = $CH_3(CH_2)_6$, R^1 = *i*-Pr	**3g**	54	–30.0	85
8	**1h**: R = *i*-PrO_2CCH_2, R^1 = *i*-Pr	**3h**	72	–34.6	93
9	**1i**: R = $BnCH_2$, R^1 = *i*-Pr	**3i**	68	–36.2	90
10[e]	**1j**: R = Bn, R^1 = *i*-Pr	**3j**	59	–6.6	84
11[e]	**1k**: R = *m*-$ClC_6H_4CH_2$, R^1 = *i*-Pr	**3k**	84	–9.7	80
12[d]	**1l**: R = *p*-$BrC_6H_4CH_2$, R^1 = *i*-Pr	**3l**	77	–11.9	80
13[e]	**1m**: R = Bn, R^1 = Et	**3m**	55	–31.1	87
14[e]	**1n**: R = *m*-$ClC_6H_4CH_2$, R^1 = Et	**3n**	63	–25.6	80
15[e]	**1o**: R = *p*-$BrC_6H_4CH_2$, R^1 = Et	**3o**	61	–25.4	85

[a] Reactions were performed on a 0.25 mmol scale. Reaction time: 3 days for entry 2; 5 days for entries 1, 4, 5, 6, 11–15; 6 days for entries 7–10; 7 days for entry 3. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] CH_2Cl_2 as the solvent. [e] –20 °C.

The thus obtained amination product **3** could be readily converted to tetrasubstituted chiral hydrazines. For example, the reaction of **3a** and acid chloride **12** could afford the corresponding chiral tetrasubstituted chiral hydrazine **13** in 47% yield without loss of enantioselectivity. Many hydrazine derivatives show remarkable biological activities, and it is a well-known structural motif in pharmaceuticals and agrochemicals.[13] For example, peptidomimetics (azapeptides) derived from hydrazine were found to be potent agents against AIDS and SARS.[13b–c] The thus obtained enantioenriched tri- or tetrasubstituted hydrazines **3** and **13** might be interesting targets in medicinal chemistry.



We also examined the reaction of α-phenylnitroacetate **1p** and DBAD, but no desired product was obtained. Since DBAD was less reactive than other azodicarboxylates,[14] we further checked if diethyl azodicarboxylate **2b** (DEAD) could react with **1p**. The amination of α-phenylnitroacetate **1p** using DEAD indeed took place. However, the best result obtained by now was to run the reaction in THF at –40 °C, which afforded product **3p** in 61% yield with only 22% ee.



In summary, we have developed the first example of catalytic asymmetric direct amination of α-monosubstituted nitroacetates using DBAD. The simple and easily available Hatakeyama's

catalyst β-ICD **11** was identified to be a highly enantioselective catalyst for reaction of α-aliphatic substituted nitroacetates with DBAD. Currently, α-phenylnitroacetate **1p** has been found to be able to work with less hindered azodicarboxylates such as DEAD, but the enantioselectivity of the corresponding product is not satisfactory. The development of new chiral bifunctional Brønsted acid–base catalysts to improve the enantioselectivity for the amination of α-arylnitroacetates is now in progress in our lab.

Acknowledgements

We thank the financial support from the National Natural Science Foundation of China (20801018, 20902025), Shanghai Pujiang Program (10PJ1403100), the Fundamental Research Funds for the Central Universities (East China Normal University 11043), Shanghai Rising-Star Program (10QA1402000) and Specialized Research Fund for the Doctoral Program of Higher Education (20090076120007).

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