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Catalytic Enantioselective Addition of Pyrazol-5-ones to Trisubstituted Nitroalkenes with an *N*-Sulfinylurea Organocatalyst

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Abstract: The first example of enantioselective nitronate protonation following Michael addition of a carbon nucleophile to an α,β,β-trisubstituted nitroalkene is reported. An *N*-sulfinylurea catalyst was employed to catalyze the addition of a variety of 3-substituted pyrazol-5-one nucleophiles to trisubstituted nitroalkenes incorporating an oxetane or azetidine ring at the β-position. The nitroalkane-pyrazolone adducts were obtained with good yield and enantioselectivity. Furthermore, the Michael addition products can be reduced to the corresponding enantioenriched amines with minimal loss of enantiomeric purity.

Keywords: asymmetric catalysis; Michael addition; nitroalkenes; organic catalysis; protonation

The nitroalkene is a versatile electrophile that has been utilized in numerous catalytic enantioselective conjugate addition reactions to access biologically relevant compounds.[1] Previously, we reported the first example of catalytic enantioselective additions of nucleophiles to α,β,β-trisubstituted nitroalkenes, which was accomplished by enantioselective protonation of the nitronate intermediate generated upon thioacid addition (Figure 1a).[2] Very recently, Jørgensen and co-workers also employed trisubstituted nitroalkene electrophiles to achieve intramolecular enantioselective nitronate additions that proceeded by trienamine catalysis (Figure 1b).[3] Here we report that enantioselective nitronate protonation following catalytic nucleophile addition to trisubstituted nitroalkenes can be extended to carbon nucleophiles with the addition of pyrazolones, a class of nitrogen heterocycles found in various biologically active molecules and dyes (Figure 1c).[4,5] For this transformation, an *N*-sulfinylurea catalyst provided the highest enantioselectivity.[6]

A key challenge for additions to trisubstituted nitroalkenes followed by enantioselective protonation is the inherent acidity of the new nitroalkane stereocenter in the product,[7] which is susceptible to epimerization by either the basic nucleophile or the tertiary amine-substituted organocatalyst. Our group has found that acidic nucleophiles buffer the reaction mixture, preventing epimerization of the nitroalkane stereocenter.[8,9]

The pyrazol-5-one is an acidic heterocycle because it becomes aromatic upon deprotonation, and therefore should be appropriate for enantioselective nitronate protonation. Numerous groups have investigated the reactivity of pyrazolones.[10] One area of investigation has been hydrogen-bonding organocatalyzed pyrazolone additions, for which excellent enantioselectivities have been achieved using β-substituted nitroalkenes (Figure 2a).[11] However, only a single example of pyrazolone nucleophile addition to an α-substituted nitroalkene has been reported (Figure 2b),[12] and here the high observed diastereoselectivity could be due to either diastereoselective protonation or epimerization of the nitroalkane product.

We began our investigation with reaction conditions that we previously used for the addition of thioacetic acid to trisubstituted nitroalkenes.[2] For our optimization studies, we chose to use oxetane nitroalkene **2a** because the oxetane ring introduces ring strain to increase the reactivity of these fully substituted nitroalkenes. Additionally, oxetanes are valued in medicinal chemistry for their ability to modulate drug properties.[13] *N*-*tert*-Butylpyrazolone **1a** was used because the *tert*-butyl group improved the solubility of the pyrazolone nucleophile. *N*-H- and *N*-phenylpyrazolones were also investigated, but were found to be only sparingly soluble, leading to poor enantioselectivity. At room temperature in cyclopentyl methyl ether (CPME), a solvent that we have often found to be optimal for hydrogen-bonding organocatalysis,[6a–d] the reaction proceeded with high conversion but low enantioselectivity for 3,5-bistrifluoromethylphenyl-

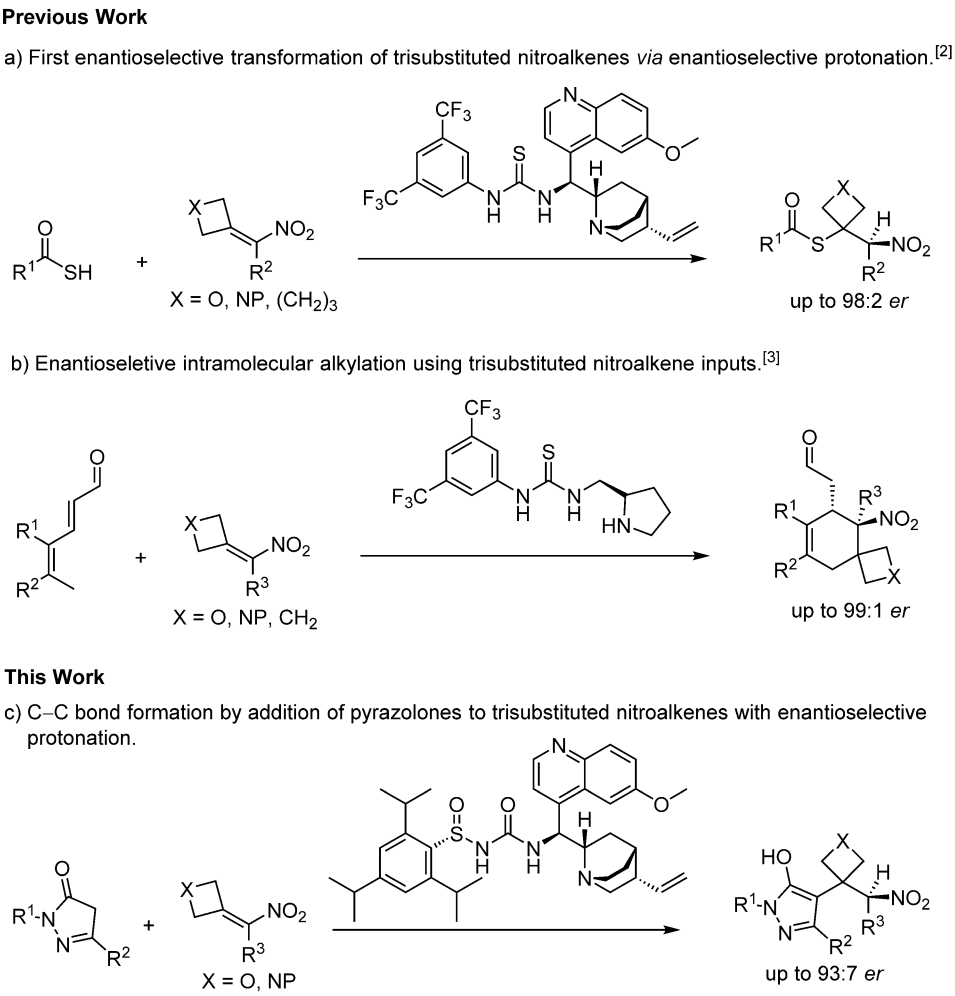


Figure 1. Enantioselective transformations of α,β,β-trisubstituted nitroalkenes.

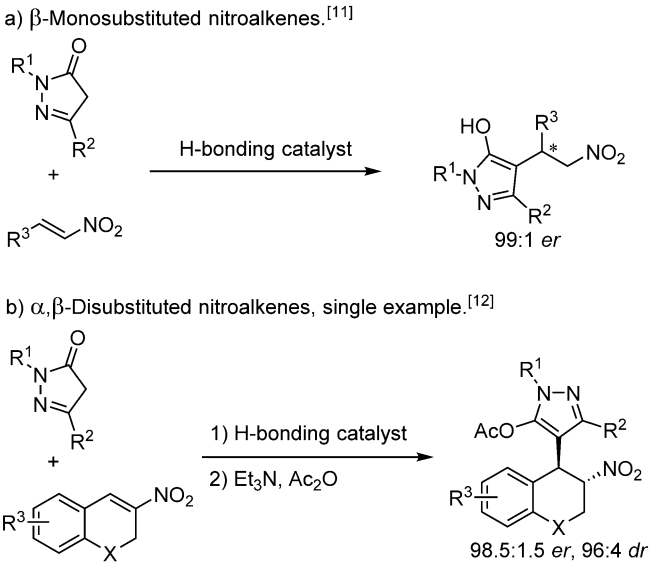


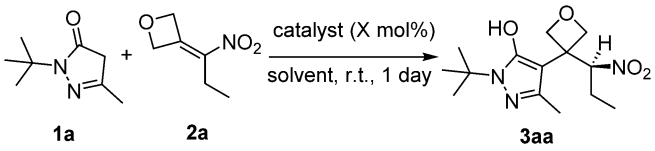
Figure 2. Reported catalytic enantioselective Michael additions of pyrazolones to nitroalkenes.

containing catalysts **4** and **5** (Table 1, entries 1 and 2).[14,15]

To improve the enantioselectivity of the transformation, we evaluated catalysts that combined a chiral *N*-sulfinyl motif with the chiral *N,N*-dimethylcyclohexane-1,2-diamine motif.[6b–d] Catalysts **6** and **7** showed a modest increase in enantioselectivity, with the all (*S*)-diastereomer providing superior enantioselectivity and conversion (entries 3 and 4). Increasing the steric bulk of the pendant tertiary amine by using piperidine catalysts **8** and **9** further improved the enantioselectivity for both catalyst diastereomers and also established that the diamine is the most significant contributor to the control of stereochemistry (entries 5 and 6).

Because bulkier amines improved the enantioselectivity, we explored other sterically encumbered chiral diamines (Figure 3). Combining the *N*-sulfinylurea motif with 9-amino(9-deoxy)epiquinine furnished catalyst **10**, which retained the enantioselectivity of the reaction, but at lower conversion (entry 7). However, when using catalyst **11**, the all (*S*)-diastereomer of **10**,

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (X mol%)	Solvent	Conversion[b]	*er*[c]
1	**4** (5)	CPME	87%	33:67
2	**5** (5)	CPME	83%	60:40
3	**6** (5)	CPME	29%	69:31
4	**7** (5)	CPME	62%	75:25
5	**8** (5)	CPME	40%	73:27
6	**9** (5)	CPME	33%	16:84
7	**10** (5)	CPME	22%	81:19
8	**11** (5)	CPME	60%	80:20
9[d]	**11** (5)	CPME	46%	86:14
10[d]	**11** (5)	dioxane	44%	91:9
11[d,e]	**11** (10)	dioxane	90%	91:9
12[d,e,f]	**11** (10)	dioxane	98%	85:15
13[d,e,g]	**11** (10)	dioxane	93%	91:9

[a] *Reaction conditions:* **1a** (0.10 mmol), **2a** (0.05 mmol) in 0.5 mL of solvent (0.1 M).
[b] Determined by ^{1}H NMR.
[c] Enantiomeric ratios were determined by HPLC analysis of the crude reaction mixture on a chiral stationary phase.
[d] Added 3 Å MS (250 mg mmol^{-1}).
[e] 2 days.
[f] Added 10 mol% of acetic acid.
[g] Added 10 mol% of benzoic acid.

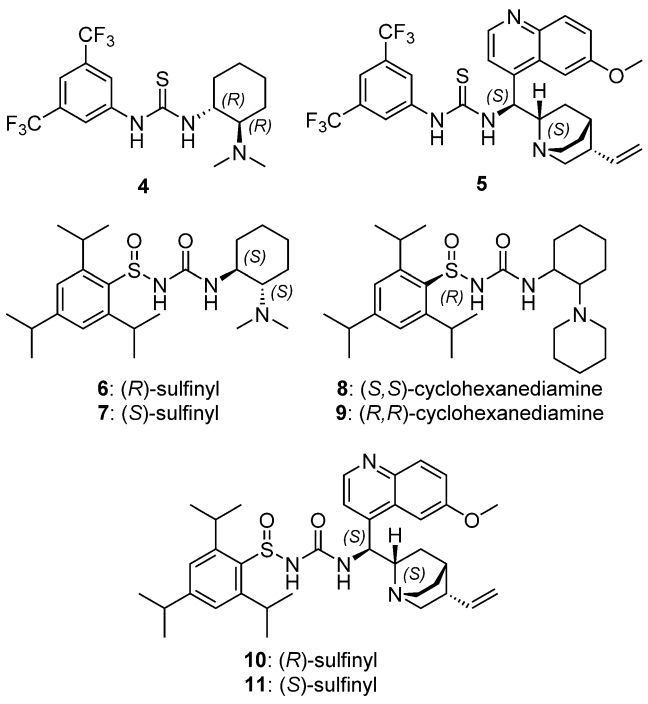


Figure 3. Bifunctional (thio)urea organocatalysts.

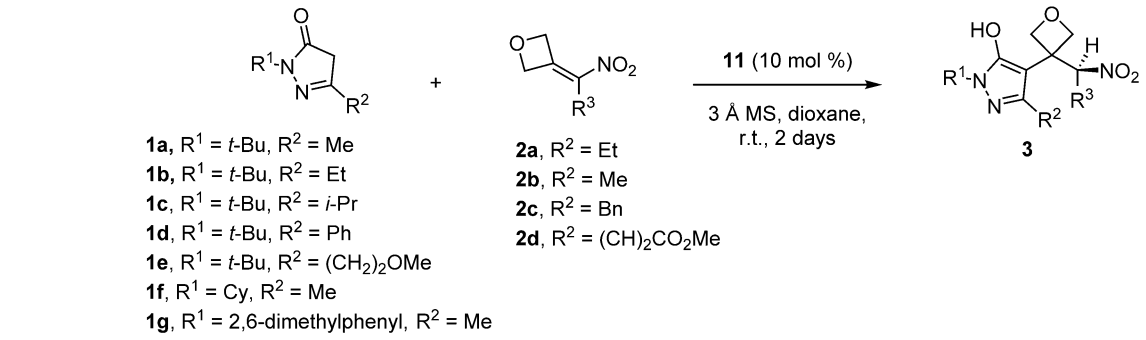
for the Michael addition, **3aa** was obtained in good conversion and enantioselectivity (entry 8). Using dioxane, a solvent in which the pyrazolone nucleophile was more soluble, and adding 3 Å molecular sieves as a desiccant further improved the enantioselectivity of the reaction to a 91:9 *er* (entries 9 and 10). A number of other solvents was also investigated, including dichloromethane, diethyl ether, THF, and toluene, but all gave lower enantioselectivities (data not shown). Increasing the catalyst loading to 10 mol% and extending the reaction time to two days provided **3aa** in 93% conversion and 91:9 *er* (entry 11). Acid additives were also investigated. The addition of 10 mol% of acetic acid improved the reaction conversion, but a lower enantioselectivity was observed (entry 12). While the addition of 10 mol% of benzoic acid did not adversely impact our model system (entry 13), it was not beneficial when used with poorer performing substrates.

With a set of optimized conditions, we explored the scope of the transformation, focusing first on the pyrazolone nucleophile **1** (Table 2). *N-tert*-Butylpyrazolones with methyl (**1a**), ethyl (**1b**), and isopropyl (**1c**) R^2 substituents all gave products with good enantioselectivity (**3aa**, **3ba** and **3ca**); however, as illustrated by **3aa** *versus* **3ca**, increasing steric bulk at R^2 resulted in lower yields due to reduced conversion. Some variability in the enantioselectivity of the reaction to form **3aa** was observed, with enantioselectivity ranging from 93:7 to 90:10 *er*. Substitution at R^2 was not limited to simple alkyl chains. When R^2 was phenyl, adduct **3da** was obtained in good yield and 82:18 *er*. A pendent methyl ether could also be incorporated to provide **3ea** in moderate yield and good enantioselectivity. Different substituents at the R^1 position of the pyrazolone were also investigated. While pyrazolones where R^1 was H or phenyl were not tolerated due to poor solubility under the reaction conditions, other R^1 substituents were compatible. *N*-Cyclohexylpyrazolone **1f** reacted to give **3fa** in good yield and 83:17 *er*. An aromatic R^1 group containing 2,6-disubstitution was also compatible, *N*-2,6-dimethylphenylpyrazolone **1g** reacted with nitroalkene **2a** to give **3ga** in moderate yield and diminished enantioselectivity.

Variation of the R^3 substituent on nitroalkene **2** was also tolerated; adduct **3bb** from nitroalkene **2b** (R^3 = Me) was isolated in acceptable yield and 90:10 *er*. Nitroalkene **2c** (R^3 = benzyl) also reacted with pyrazolones **1b** and **1c** to give **3bc** and **3cc**, respectively. Additionally, a pendent ester could be incorporated at R^3 to provide product **3ad**, although a decrease in enantioselectivity was observed.

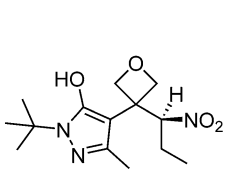
The transformation is not limited to oxetane nitroalkenes, but also proceeds in good yields and enantioselectivity for azetidine nitroalkenes (Table 3). Multiple nitrogen protecting groups were tolerated on the azetidine nitroalkenes. Pyrazolone **1a** added to *N*-Boc

Table 2. Oxetane substrate scope.[a]

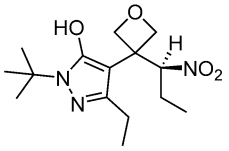


1a, R^1 = *t*-Bu, R^2 = Me
1b, R^1 = *t*-Bu, R^2 = Et
1c, R^1 = *t*-Bu, R^2 = *i*-Pr
1d, R^1 = *t*-Bu, R^2 = Ph
1e, R^1 = *t*-Bu, R^2 = $(CH_2)_2OMe$
1f, R^1 = Cy, R^2 = Me
1g, R^1 = 2,6-dimethylphenyl, R^2 = Me

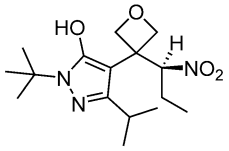
2a, R^2 = Et
2b, R^2 = Me
2c, R^2 = Bn
2d, R^2 = $(CH)_2CO_2Me$



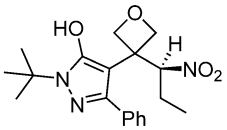
3aa
61% yield, 93:7–90:10 *er*



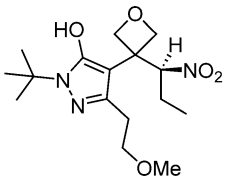
3ba
58% yield, 89:11 *er*



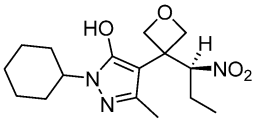
3ca
32% yield, 93:7 *er*



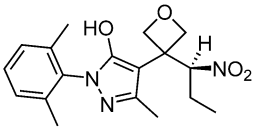
3da
84% yield, 82:18 *er*



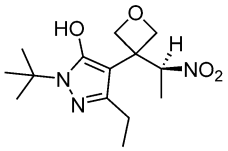
3ea
66% yield, 89:11 *er*



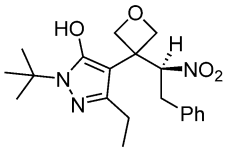
3fa
84% yield, 83:17 *er*



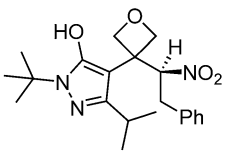
3ga
64% yield, 72:28 *er*



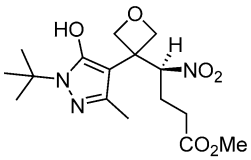
3bb
50% yield, 90:10 *er*



3bc
66% yield, 87:13 *er*



3cc
42% yield, 85:15 *er*

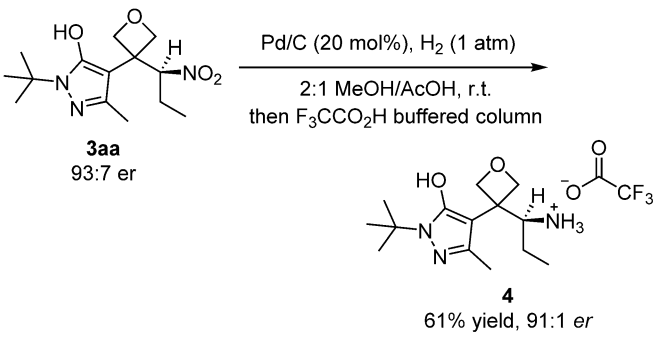


3ad
71% yield, 76:24 *er*

[a] *Reaction conditions:* **1** (2 equiv.), **2** (1 equiv.), **11** (10 mol%), 3 Å MS (250 mg mmol^{-1}) in dioxane (0.1 M). Yields are of isolated product after chromatography. Enantiomeric ratios of isolated products were determined using HPLC analysis on a chiral stationary phase.

(**2e**), *N*-Cbz (**2f**), and *N*-Ts (**2g**) azetidine nitroalkenes with good enantioselectivity. Additionally, *N*-Boc and *N*-Cbz products (**3ae** and **3af**) were isolated in good yields. Methylpyrazolone **1a** also added to *N*-Boc-azetidine nitroalkene **2h** (R^3 = Bn) to give **3ah** in good yield and enantioselectivity. Upon decreasing the steric bulk of R^2 from methyl to H, an expected increase in yield was observed, although the enantioselectivity of the reaction was also diminished (**3he**). Nitroalkenes lacking ring strain at the β-position were also explored, but were found to be unreactive.

To demonstrate the ability to access chiral amines from the addition products, we explored selective reduction of the nitro group in **3aa**. Using Pd/C and hydrogen at atmospheric pressure, the nitroalkane was selectively reduced in the presence of the pyrazol-5-ol heterocycle. After purification using a trifluoroacetic acid (TFA) buffered column, amine **4** was isolated as the TFA salt in 61% yield with minimal reduction of enantiopurity (Scheme 1). To determine the sense of

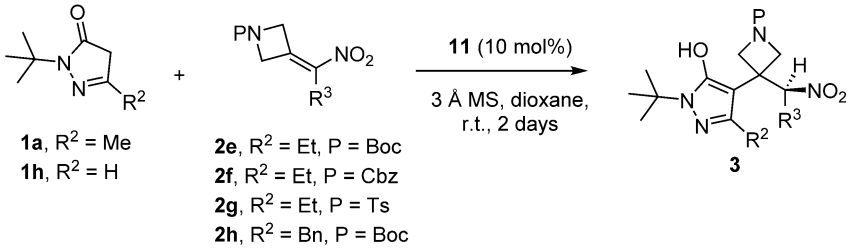


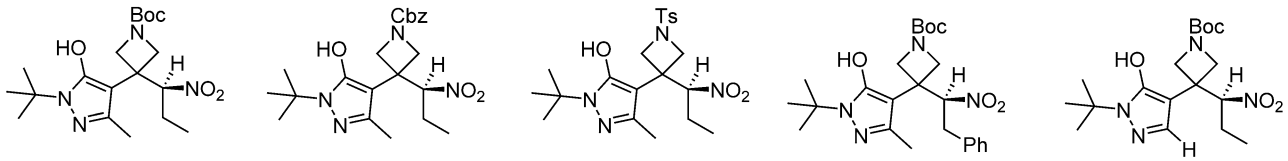
3aa
93:7 er

4
61% yield, 91:1 *er*

Scheme 1. Reduction of enantioenriched **3a**.

Table 3. Azetidine substrate scope.[a]





[a] Reaction conditions: **1** (2 equiv.), **2** (1 equiv.), **11** (10 mol%), 3 Å MS (250 mg mmol^{-1}) in dioxane (0.1 M). Yields are of isolated product after chromatography. Enantiomeric ratios of isolated products were determined using HPLC analysis on a chiral stationary phase.

induction, we performed Mosher amide analysis on **4** and have tentatively assigned the stereochemistry to be (*S*).[16,17]

In conclusion, we have developed a catalytic enantioselective addition of pyrazolones to trisubstituted nitroalkenes using a bifunctional *N*-sulfinylurea organocatalyst. This transformation is the first example of a Michael addition of a carbon nucleophile to a trisubstituted nitroalkene followed by enantioselective nitronate protonation. Additional catalytic enantioselective additions to trisubstituted nitroalkenes will be the subject of future investigations.

Experimental Section

Representative Procedure

A flame-dried 4-mL vial equipped with stir bar and open top screw cap with a pierceable PTFE/silicone rubber septum was charged with pyrazolone **1** (0.50 mmol, 2 equiv.), catalyst **11** (0.025 mmol, 10 mol%), and 3 Å molecular sieves (62 mg). Under a positive pressure of N_2, anhydrous dioxane (1.5 mL) was added to the vial followed by a nitroalkene **2** in dioxane solution (1.0 mL, [nitroalkene = 0.25 M], 0.25 mmol, 1 equiv.). After stirring for 2 days at room temperature, the reaction mixture was chilled in a 0 °C ice bath for 1 min, and then the reaction was quenched with 0 °C 5% (v/v) trifluoroacetic acid in CPME. The crude mixture was immediately eluted through a silica plug with ethyl acetate and the resulting solution was concentrated under vacuum. The crude product was purified by column chromatography and the enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase.

Acknowledgements

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