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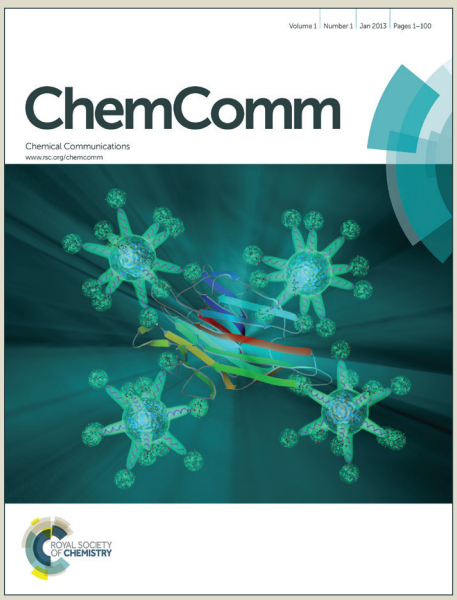

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Enantioselective Formal α-Allylation of Nitroalkanes through Chiral Iminophosphorane–Catalyzed Michael Reaction/Julia–Kocienski Olefination Sequence†

Cite this: DOI: 10.1039/c3cc00000x

Received 00th January 2013,
Accepted 00th January 2013

DOI: 10.1039/c3cc00000x

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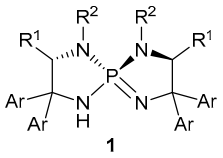
Daisuke Uraguchi,[a] Shinji Nakamura,[a] Hitoshi Sasaki,[a] Yuki Konakade,[a] and Takashi Ooi*[a,b]

A two-step sequence for the asymmetric formal α-allylation of nitroalkanes is disclosed. This new methodology relies on the development of a highly diastereo- and enantioselective conjugate addition of nitroalkanes to vinylic 2-phenyl-1*H*-tetrazol-5-ylsulfones using chiral triaminoiminophosphorane as a requisite base catalyst and subsequent Julia-Kocienski olefination under kinetic conditions.

Stereoselective α-functionalization of nitroalkanes offers an attractive yet powerful tool for the preparation of various chiral organic molecules having functionalities that can be derived from the nitro group.[1] Accordingly, the development of reliable catalytic protocols constitutes a vital area in organic synthesis, and significant progress has been made in attaining sufficient reactivity and selectivity in the addition of nitroalkanes to carbonyls, imines, and electron-deficient unsaturated bonds.[2] However, simple alkylation of nitroalkanes to access α-chiral nitro compounds has been regarded as a problematic reaction, primarily because of the ambident reactivity of the intermediary generated nitronates. Namely, *O*-alkylation of nitronates is generally favored over *C*-alkylation under the standard basic conditions, and single-electron-transfer process is known to be a prerequisite for implementing the selective *C*-alkylation.[3] In fact, currently available methods for the stereoselective α-alkylation of nitroalkanes are restricted to asymmetric allylic alkylation catalyzed by chiral transition-metal complexes with limited substrate scope and moderate stereoselectivities.[4,5] In the context of pursuing an alternative approach to address this long-standing problem, we became interested in the possibility of establishing a formal asymmetric α-alkylation of nitroalkanes by the judicious combination of a stereoselective conjugate addition to vinylic sulfones, specifically 2-substituted 1-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)ethenes **2**, and subsequent Julia-Kocienski olefination.[6-8] The total lack of catalytic systems that enable rigorous absolute and relative stereocontrol in the Michael-type reaction of nitroalkanes with vinylic sulfones posed a great challenge;[9,10] nonetheless we envisaged that the use of *P*-spiro chiral triaminoiminophosphoranes **1** (Fig. 1) as a catalyst could pave the way for our objective, considering the ability of their conjugate acids **1**·H to precisely recognize reactive nitronates through hydrogen-bonding-assisted ionic interactions.[11-14] Herein, we report the development of the highly diastereo- and enantioselective conjugate addition of nitroalkanes to vinylic sulfones **2** under the influence of **1** and the marriage of this new protocol with Julia-Kocienski olefination, thereby providing a flexible stereoselective route to α-alkylated chiral nitroalkanes.



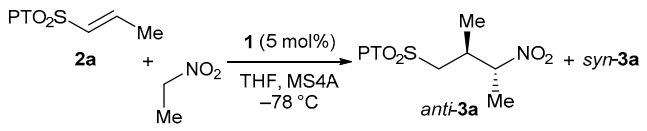
1

1a: Ar = Ph, R^1 = ^{i}Pr, R^2 = Me
1b: Ar = Ph, R^1 = (*S*)-^{s}Bu, R^2 = Me
1c: Ar = 4-FC_6H_4, R^1 = (*S*)-^{s}Bu, R^2 = Me
1d: Ar = 4-MeC_6H_4, R^1 = (*S*)-^{s}Bu, R^2 = Me
1e: Ar = Ph, R^1 = (*S*)-^{s}Bu, R^2 = Et

Figure 1 *P*-Spiro chiral triaminoiminophosphoranes

The investigation was initiated by conducting the addition of nitroethane to 1-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)propene (**2a**) in THF at –78 °C in the presence of L-valine-derived iminophosphorane **1a** (5 mol%) as the catalyst. The reaction proceeded smoothly to give the conjugate addition product **3a** in good yield with a diastereomeric ratio of 10:1, but the enantiomeric excess of the major product *anti*-**3a** was revealed to be rather low (Table 1, entry 1). This result prompted us to examine the effect of the catalyst structure mainly on the selectivity profile. Interestingly, changing the alkyl side chain of the parent amino acid origin (R^1) from isopropyl to (*S*)-*sec*-butyl group (**1b**) led to a dramatic improvement of the stereoselectivity, and *anti*-**3a** was predominantly obtained with a high level of enantiocontrol (entry 2). On the other hand, a certain decrease in the diastereo- or enantioselectivity was observed when 4-fluoro- (**1c**) or 4-methylphenyl (**1d**) groups were introduced as aromatic substituents (Ar), irrespective of their electronic properties (entries 3 and 4). Eventually, further structural tuning of **1** by the replacement of the *N*-methyl appendage (R^2) with an ethyl group (**1e**) afforded a critical enhancement of the stereoselectivity, resulting in the exclusive formation of *anti*-**3a** with 95% ee (entry 5).

Table 1 Optimization of catalyst (PT = 1-phenyl-1*H*-tetrazol-5-yl)[a]

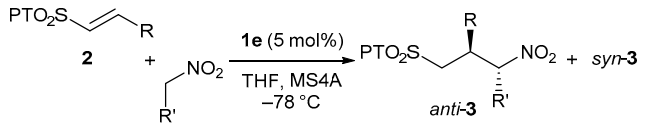


entry	1	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	6	89	10:1	28
2	**1b**	7	75	14:1	92
3	**1c**	20	80	9:1	92
4	**1d**	24	68	10:1	86
5	**1e**	16	83	>20:1	95

[a] The reaction was performed with 0.1 mmol of **2a**, 1.0 mmol of nitroethane, and 5 mol% of **1** in THF (1.0 mL) with MS4A (100 mg) at –78 °C. See ESI† for details. [b] Isolated yield. [c] Diastereomeric ratios were determined by 400 MHz ^{1}H NMR analysis of crude aliquots. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute configuration of **3a** was assigned by analogy to **3h**.

With the optimal catalyst structure in hand, we studied the substrate scope of this new asymmetric conjugate addition protocol; the representative results are listed in Table 2. In general, 5 mol% of **1e** was sufficient for the reaction to be completed within 24 h, and the presence of 4A molecular sieves was crucial for efficient catalyst turnover. With 2-alkyl-substituted vinylic sulfones, the present system tolerated not only the elongation of simple carbon chains but also the incorporation of various functional groups, and good-to-excellent stereoselectivities were uniformly observed (entries 1–6).

Table 2 Substrate scope (PT = 1-phenyl-1*H*-tetrazol-5-yl)[a]



entry	R	2	R'	time (h)	yield (%)[b]	dr[c]	ee (%)[d]	3
1	Et	**2b**	Me	11	99	>20:1	94	**3b**
2	$Me(CH_2)_7$	**2c**	Me	12	99	>20:1	95	**3c**
3	CH_2=$CH(CH_2)_8$	**2d**	Me	7	92	>20:1	95	**3d**
4	$BnO(CH_2)_3$	**2e**	Me	20	84	19:1	97	**3e**
5	$BzO(CH_2)_3$	**2f**	Me	10	95	12:1	95	**3f**
6[e]	$PhthN(CH_2)_3$[f]	**2g**	Me	24	99	>20:1	94	**3g**
7	Ph	**2h**	Me	15	93	>20:1	88	**3h**
8	*o*-FC_6H_4	**2i**	Me	9	95	12:1	80	**3i**
9[e]	*m*-MeC_6H_4	**2j**	Me	17	99	>20:1	87	**3j**
10	*m*-BrC_6H_4	**2k**	Me	6	99	13:1	90	**3k**
11[e]	*p*-MeC_6H_4	**2l**	Me	21	98	>20:1	87	**3l**
12	*p*-ClC_6H_4	**2m**	Me	6	91	19:1	83	**3m**
13[e]	2-Naph	**2n**	Me	6	99	>20:1	93	**3n**
14	$Me(CH_2)_7$	**2c**	Et	18	99	>20:1	85	**3o**

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2**, 1.0 mmol of nitroalkane, and 5 mol% of **1e** in THF (1.0 mL) with MS4A (100 mg) at –78 °C. See ESI† for details. [b] Isolated yield. [c] Diastereomeric ratios were determined by 400 MHz ^{1}H NMR analysis of crude aliquots. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute configuration of **3h** was determined by X-ray diffraction analysis and others were assigned by analogy to **3h**. [e] 0.5 mL of THF was used. [f] PhthN = phthaloylimide.

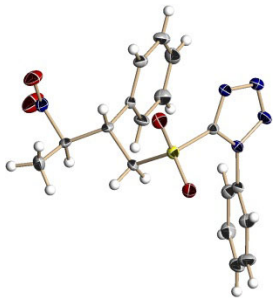
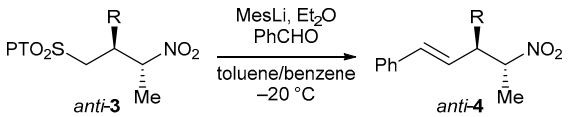


Figure 2 ORTEP diagram of *anti*-**3h**. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon.

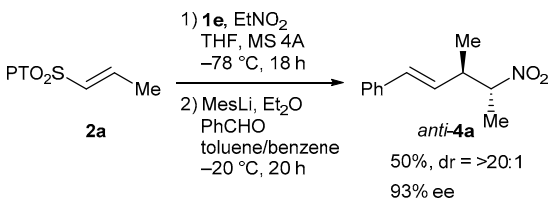
While 2-aryl-substituted vinylic sulfones also appeared to be good Michael acceptors, the enantioselectivity of the *anti*-isomer was affected by the steric and electronic properties of the aromatic substituents, though it remained at a synthetically useful level (entries 7–13). In addition, a comparable degree of stereochemical control was achieved in the reaction with nitropropane as a donor substrate (entry 14).[15] The absolute configuration of *anti*-**3h** was unambiguously determined to be 2*S*,3*R* by single crystal X-ray diffraction analysis (Fig. 2), and the stereochemistries of other examples were assumed by analogy.

Having realized the desired catalytic Michael technology with high stereocontrol, we explored the appropriate conditions for performing the Julia-Kocienski olefination of *anti*-**3** without loss of stereochemical integrity. In consideration of the low pK_a value of the α-proton of the nitro functionality, almost diastereomerically pure *anti*-**3a** and **3h** were treated with the bulky mesityllithium in the presence of benzaldehyde, respectively, for ensuring kinetic deprotonation at the α-position of the sulfonyl moiety (Scheme 1). As expected, formally α-allylated nitroalkanes *anti*-**4a** and **4h** were obtained in good yields and preservation of the enantiomeric excess of



3a (R = Me): dr = >20:1, 95% ee **4a** (R = Me): 72%, dr = >20:1, 95% ee
3h (R = Ph): dr = >20:1, 88% ee **4h** (R = Ph): 82%, dr = >20:1, 87% ee

Scheme 1 Julia-Kocienski olefination of *anti*-**3** to demonstrate formal α-allylation of nitroalkanes (PT = 1-phenyl-1*H*-tetrazol-5-yl)



Scheme 2 One-pot Operation of Chiral Iminophosphorane **1e**–Catalyzed Michael Reaction/Julia–Kocienski Olefination Sequence (PT = 1-phenyl-1*H*-tetrazol-5-yl)

each product was confirmed by HPLC analysis. Furthermore, we found that one-pot operation of the consecutive **1e**-catalyzed Michael reaction/olefination sequence was feasible with retention of high stereoselectivity as exemplified in Scheme 2.

In conclusion, a two-step sequence for the asymmetric formal α-allylation of nitroalkanes was established through the development of a highly stereoselective conjugate addition of nitroalkanes to vinylic 2-phenyl-1*H*-tetrazol-5-ylsulfones, utilizing chiral triaminoiminophosphorane as an organic base catalyst and subsequent Julia-Kocienski olefination under kinetic conditions. This method represents an alternative yet reliable solution to the problem associated with the enantioselective α-alkylation of nitroalkanes and thus offers access to a variety of α-alkylated chiral nitroalkanes.

This work was supported by NEXT program, JST-CREST, a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT, Program for Leading Graduate Schools "Integrative Graduate Education and Research Program in Green Natural Sciences" in Nagoya University, the Asahi Glass foundation, and Grants of JSPS for Scientific Research. S.N. acknowledges JSPS for financial support.

Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of **1e**~**4**, absolute structure determination of *anti*-**3h**. See DOI: 10.1039/c3cc00000x/

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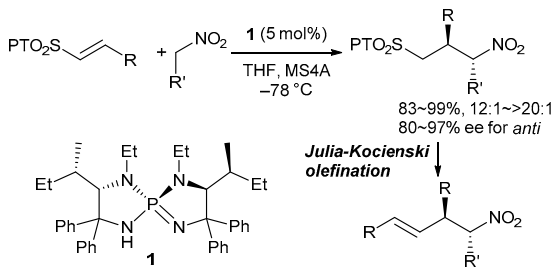
15 The present system is sensitive to the steric nature of nitroalkanes, and the reactions with α- or β-branched nitroalkanes are rather sluggish even at higher temperature.

Graphical Abstracts



Enantioselective Formal α-Allylation of Nitroalkanes through Chiral Iminophosphorane Catalyzed Michael Addition/Julia–Kocienski Olefination Sequence

Daisuke Uraguchi, Shinji Nakamura, Hitoshi Sasaki, Yuki Konakade, and Takashi Ooi*

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