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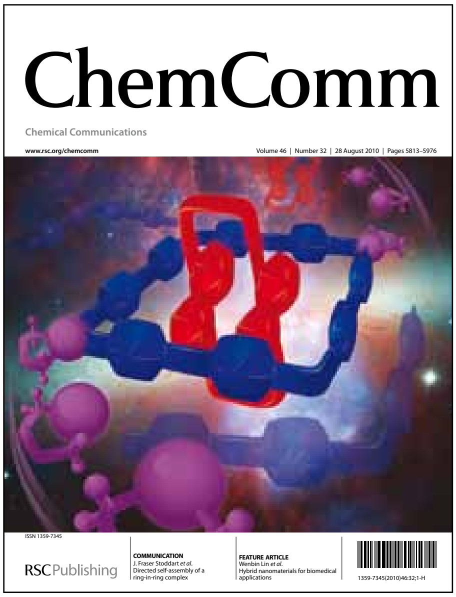

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Cascade Functionalization of Unsaturated Bond-Containing Polymers Using Ambident Agents Possessing both Nitrile *N*-Oxide and Electrophilic Functions

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We developed a powerful and highly reliable cascade functionalization technique for constructing sophisticated macromolecular architectures. Central to the technique are the ambident agents having combined functions of a nitrile *N*-oxide group and an electrophile. The agents proved capable of facile catalyst- and solvent-free functionalization of polymers and further integrations involving cross-linking.

Cascade functionalization[1] of macromolecules based on the Cu-catalyzed Huisgen cycloaddition[2] of azides to alkynes has generated particular interests as a powerful method for molecular integration of polymers. The method has been widely adopted for the constructiokn of highly sophisticated macromolecular architectures such as graft polymers, bioconjugated polymers, functional surface, and cross-linked polymers, due to the simple procedure and the high reaction efficiency.[3] However, the explosiveness of azides and the requirement of a Cu catalyst have limited its use.[4] In addition, the method also limits the polymer versatility because it requires the introduction of alkyne or azide functionality into the trunk polymer in advance.

Intrigued by these techniques but mindful of their limitations, we undertook the development of a more versatile, powerful, and byproduct-free functionalization method, optimally one that could enable large-scale macromolecular synthesis.

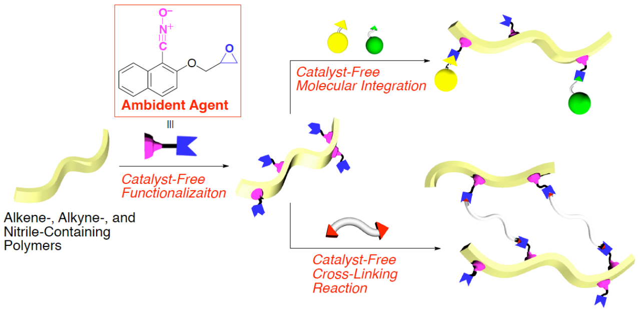
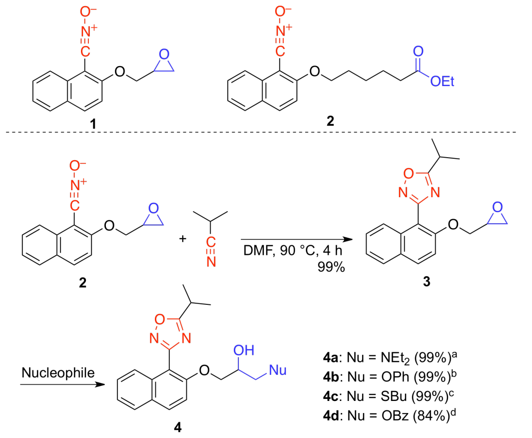


Fig. 1 Schematic representation of a new cascade functionalization using an ambident agent having nitrile *N*-oxide and electrophilic functions.

We envisioned that, if various unsaturated bonds, including internal olefin and CN groups with relatively low reactivity, are available, functionalization should enable modification and cross-linking of many unsaturated bond-containing polymers such as natural rubber, synthetic rubbers, and CN-containing polymers. It should also provide new pathways to development of chemical products made from polymers such as micelle, fiber, sheet, and film that serve as reactive scaffolds for molecular integration.

Herein, we introduce a new cascade functionalization technique involving use of an ambident agent (Fig. 1). We describe the model functionalization reaction of the agent, with both nitrile *N*-oxide[5] and electrophilic functions, and investigate the application of the technique to polymer modification.

Building on our previous work,[6] we synthesized epoxide- and ester-containing ambident agents (**1** and **2**, Scheme 1)[7] and the structures of **1** and **2** were determined by ^{1}H NMR, ^{13}C NMR, IR, and FAB HRMS measurements.[7]



Scheme 1 Structures of ambident agents (**1** and **2**) and the model ligation reaction of **1** with isobutyronitrile and various nucleophiles. *Reagents and Conditions*: a) Et_2NH (1.05 equiv), $CHCl_3$, 50 °C, 2 d; b) PhOH (1.05 equiv), K_2CO_3 (1.3 equiv), DMF, 120 °C, 12 h; c) BuSH (1.05 equiv) K_2CO_3 (1.3 equiv), DMF, 120 °C, 12 h; d) PhCOOH (1.05 equiv), TBAB (3 mol%), CH_3CN, reflux, 1 d.

Before investigating the use of **1** as a general tool for implementing polymer reactions, we performed a model reaction of **1** with isobutyronitrile and various nucleophiles as shown in Scheme 1. Treatment of **1** with isobutyronitrile in DMF at 90 °C without any catalyst afforded oxadiazole **3** as a single isomer in quantitative yield. The regiochemistry of the oxadiazole moiety of **3** was confirmed by the characteristic signals of the 1,2,4-

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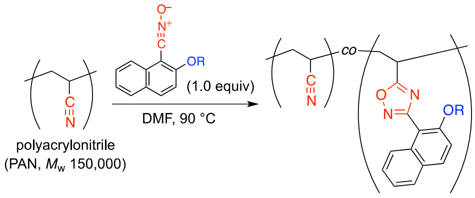
† Electronic Supplementary Information (ESI) available: [Synthesis of ambident agents (**1** and **2**), typical cascade functionalization of polymers, IR, ^{1}H NMR, ^{13}C NMR, and FAB-HR-MS spectra data.]. See DOI: 10.1039/b000000x/

oxadiazole in the ^{13}C NMR spectrum.[7] Subsequent catalyst-free nucleophilic attack at the terminal epoxy moiety of **3** was examined using various nucleophiles. Treatment with a nucleophile Et_2NH in particular gave the corresponding adduct **4a** in 99% yield without any catalyst. Similarly, nucleophiles such as phenol and thiol gave **4b** and **4c** in quantitative yields in the presence of K_2CO_3, whereas the treatment with benzoic acid afforded **4d** in the presence of TBAB[8] in 84% yield. These results strongly indicate the usefulness of **1** as a cascade functionalization tool for integrating various functionalities on the unsaturated bond-containing materials.

To clarify the time-dependent conversion of **1**, we performed the polymer reactions using polyacrylonitrile (PAN), as summarized in Table 1. The reaction in DMF using 1.0 equiv of **1** per repeating unit of PAN resulted in the formation of polyoxadiazole (Scheme 2 and Table 1). The reaction proceeded efficiently with the increase in reaction time but achieved only up to *ca.* 50% conversion, probably for two reasons: (i) the reaction rate obeys inherently the second-order kinetics depending on both concentrations of the remaining CN moieties on the main chain and **1**, and (ii) steric repulsion around the main chain increases with increase in conversion of the resulting polymer (entries 1–4). The reaction of ester-containing ambident agent **2**, which is bulkier than **1**, was carried out for comparison to actually afford the corresponding polymer in a moderate conversion yield (37%, entry 5).



Scheme 2 Functionalization of PAN with **1** and **2**.

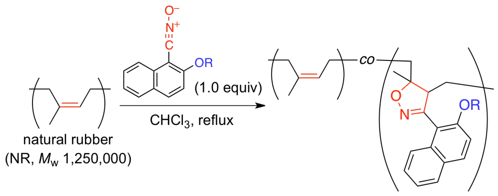
Table 1 Functionalization of PAN using ambident agents **1** and **2**.

entry	reagent	time (h)	yield (%)[a]	conversion (%)[b]
1	**1**	1	99	18
2	**1**	4	98	32
3	**1**	24	99	50
4	**1**	96	98	53
5	**2**	24	74	37

[a] MeOH-insoluble part. [b] Estimated by ^{1}H NMR.

Next, we performed the polymer reaction using natural rubber (NR) as a representative internal-olefin-containing polymer, as shown in Scheme 3. Cycloaddition reaction using 1.0 equiv of **1** per the repeating unit of NR proceeded efficiently to afford the corresponding functionalized NR with a time-dependent conversion ratio of up to *ca.* 50% (Table 2, entries 1–4). By the considerable effort, we noticed that nitrile *N*-oxide **1** gradually isomerized to the isocyanate at high temperature under the reaction conditions,[9] and twice additions of a portion of **1** (1.0 equiv) after 24 h and 48 h led to quantitative conversion yield (entry 5). For comparison, reaction with **2** afforded ester-containing NR in 30% conversion yield (entry 6).

These results prompted us to theorize that solvent-free reaction not only enables rapid conversion but should also be ideal for large-scale macromolecular synthesis. To prove this idea, we performed the polymer reaction without any solvent, press-grinding the reactants in a mortar (Table 3). To our pleasant surprise, press-grinding NR with powdery **2** at 70 °C for 1 h afforded the nitrile *N*-oxide adduct in 26% conversion yield (entry 1). In addition, prolonged reaction time to 2 h increased the conversion yield to 42% (entry 2), clearly suggesting the remarkable acceleration of the cycloaddition reaction. Similarly, polymer reactions of two commercially available elastomers, acrylonitrile–butadiene rubber (NBR) and ethylene–propylene–diene terpolymer (EPDM), gave the corresponding polymers in high conversion yields (entries 3 and 4).



Scheme 3 Functionalization of NR with **1** and **2**.

Table 2 Functionalization of NR using ambident agents **1** and **2**.

entry	reagent	time (h)	yield (%)[a]	conversion (%)[b]
1	**1**	1	99	3
2	**1**	2	99	8
3	**1**	24	98	43
4	**1**	96	99	49
5[c]	**1**	72	>99	>99
6	**2**	24	99	30

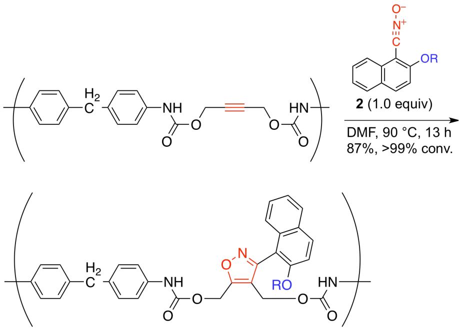
[a] MeOH-insoluble part. [b] Estimated by ^{1}H NMR. [c] The reaction was carried out with **1** (1.0 equiv). After 24 h and 48 h, the additional portions of **1** (1.0 equiv) were added to the mixture.

Table 3 Functionalization of various polymers with **2** under solvent-free conditions.

entry	polymer	time (h)	yield (%)[a]	conversion (%)[b]
1	NR	1	99	26
2	NR	2	96	42
3	NBR	1	76	olefin: >99, CN: 71
4	EPDM	1	92	35

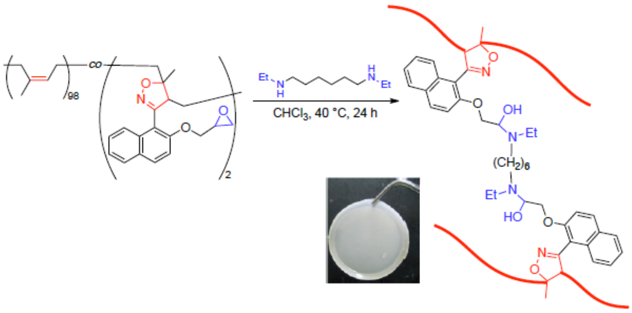
[a] MeOH-insoluble part. [b] Estimated by ^{1}H NMR.

To demonstrate the versatility of such ambident agents, we prepared an internal alkyne-containing polyurethane and performed the polymer reaction with **2**. As a result, the cycloaddition reaction using 1.0 equivalent of **2** underwent smoothly to afford the corresponding isoxazole-containing polymer in a quantitative conversion yield (Scheme 4), strongly suggesting both the chemoselectivity of **2** independent on the presence of acidic urethane N-H and the high reactivity of **2** with internal alkynes.[6i]



Scheme 4 Functionalization of internal alkyne-containing polymer with **2**.

With these electrophile-containing elastomers in hand, we demonstrated the cross-linking reaction using a ditopic nucleophile. To evaluate mechanical properties, we performed the cross-linking reaction using a $CHCl_3$ solution of NR possessing just 2% epoxy functionality with various amounts of *N*,*N*-diethylhexanediamine in a Teflon vessel. Reaction at 40 °C for 24 h gave cross-linked NR as a translucent sheet (Scheme 5). The density of the network chain, the cross-linking ratio of the resulting polymers, and the conversion yield of the diamine were estimated using a modified Flory–Rehner equation[10] based on the swelling ratio of the polymer in toluene (Table 4).



Scheme 5 Cross-linking of NR.

Table 4 Effect of diamine feed ratio on the properties of cross-linked NR.

entry	cross-linker (%)	swelling ratio (%)[a]	degree of cross-link (%)[b]	yield (%)	T_{d5} (°C)
ref.	–	–	–	–	345
1	5	930	0.41	87	338
2	25	540	1.2	98	340
3	50	380	2.5	99	340

entry	T_g (°C)	tensile strength (MPa)[c]	elongation (%)[d]	Young's Modulus (MPa)[e]
ref.	–65	6.34	1100	0.62
1	–57	–[f]	–[f]	–[f]
2	–57	5.04	698	0.50
3	–56	5.20	452	0.86

[a] Swelled by soaking in toluene overnight. [b] Estimated by modified Flory–Rehner equation. [c] Value of the stress maxima. [d] Value of the strain maxima. [e] Estimated from the slope in the range from 0 to 100% strain. [f] Not estimated.

Two findings obtained have clearly suggested the high efficiency of the epoxy functionality in the polymer: (i) the cross-linking ratio increases with increase in feed ratio of the diamine and (ii) the cross-linking reaction efficiency is sufficiently high. Thermal properties such as decomposition temperature (T_{d5}) and glass transition temperature (T_g), evaluated by differential scanning calorimetry (DSC) and thermogravimetry (TGA), reveal that all cross-linked polymers appeared at the same temperature region, probably because the ingredients in the polymers were essentially identical except for the amount of diamine spacer. Stress–strain curves for the network polymers are consistent with the feed ratio of the diamine cross-linker.

From measurements of ultimate tensile strength and elongation, we calculated Young's modulus on the basis of Hooke's law.[7] For the cross-linked NRs, stress clearly increases and strain decreases with increasing feed ratio of the diamine spacer. This result is in a good agreement with the observed swelling behavior.

In conclusion, we have designed and constructed a facile and widely applicable cascade functionalization technique for use between polymers with unsaturated bonds such as C≡N, internal C=C, and C≡C bonds and various nucleophiles via catalyst- and solvent-free 1,3-dipolar cycloadditions and subsequent byproduct-free nucleophilic reaction. The new ambident agents central to this technique show promise as a means for creating versatile polymer materials in such domains as shape-retaining surface modification of cross-linked polymers, adhesion between incompatible soft interfaces or between organic and inorganic interfaces, and novel molecular integrations using highly processed plastics made from ubiquitous polymers as the scaffold.

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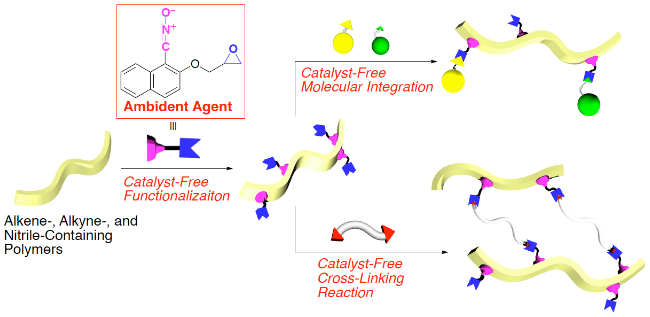
Graphical Abstract

Cascade Functionalization of Unsaturated Bond-Containing Polymers Using Ambident Agents Possessing both Nitrile *N*-Oxide and Electrophilic Functions



A new cascade functionalization technique of unsaturated bond-containing polymers was developed by using ambident agents having nitrile *N*-oxide and electrophiles.