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Alkyl transfer from C–C cleavage: replacing the nitro group of nitro-olefins†

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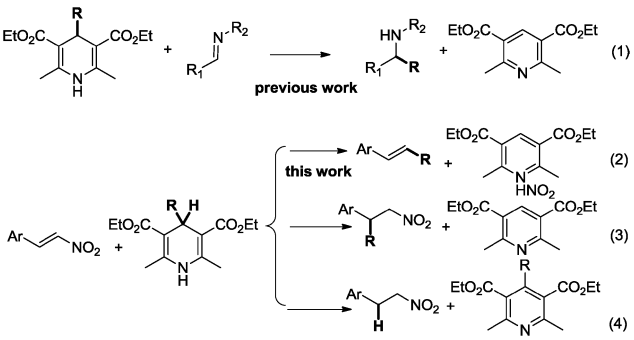
Alkyl substituted Hantzsch esters are rationally used as alkylation reagents to replace the nitro groups of nitro olefins to give excellent yields of *trans*-olefins. The reaction mechanism is considered to proceed through a free radical mechanism, which is different from the corresponding transfer alkylation of imines.

Methods for C–C bond formation are basic tools for synthetic chemists. In spite of the myriad methods available,[1] alternative metal-free green chemistry routes for C–C bond formation, in terms of operational simplicity and functional-group tolerance, are in constant demand.[2] The highly efficient natural biochemical pathways to produce complex molecules are a good source of inspiration for chemists.[3] Examination of the chemical building blocks, modes of substrate activation, and biosynthetic pathways in nature provide much insight to achieve many biomimetic organocatalytic C–C bond formations.[4]

Hantzsch esters (HEH) are bio-inspired hydride donors, commonly known as synthetic analogues of reduced nicotinamide adenine dinucleotide (NADH). Taking advantage of their special hydrogen transfer properties, a broad range of transfer hydrogenations can be conducted.[5] However, the study of alkyl transfer in this way has never been addressed until recent work by our group.[6] Similar to the corresponding transfer hydrogenation, high efficiency C-4 alkyl substituted DHPs were rationally designed for the alkylation of imines (Scheme 1, eqn (1)). Meanwhile, we put forward a reasonable stepwise concerted reaction mechanism. However, the transfer scope was limited to benzyls, secondary alkyl groups and tertiary alkyl groups. Here, we give another type of alkyl transfer in which alkyl substituted Hantzsch esters could effectively cleave the C–C bond to provide alkyl radicals that replace the nitro groups of nitro olefins



Scheme 1 Alkyl transfer with alkyl substituted DHPs.

(Scheme 1, eqn (2)). In fact, 1,4-cyclohexadiene derivatives have already been used as all sorts of radical precursors including alkyl radicals.[7] However, the efficiency of alkyl radicals provided by direct splitting of C–C bonds was very low.[7i]

It has been proved that β-nitrostyrenes are versatile building blocks which could be selectively reduced by HEH through hydrogen transfer.[8] Based on this information we have tried the corresponding alkylation at the beginning of reaction (Scheme 1, eqn (3)). Apparently, this alkyl transfer reaction was difficult to anticipate for the following reasons: (1) the competitive hydrogen transfer reaction (Scheme 1, eqn (4)), (2) the transfer mechanism was unknown which may proceed through a concerted process[9] or a free radical process.[10] For example, DHP analogue 1-benzyl-1,4-dihydronicotinamide (BNAH) was used as a reagent for replacing aliphatic nitro groups by hydrogen through a single electron transfer chain process. Moreover, it was also discovered that substitution of β-nitrostyrenes to generate corresponding alkenes was facilitated by an electrophilic carbon-centered radical process.[11]

Our study of alkyl transfer started with the hypothesis that DHPs with two alkyl groups at the C4 position should only transfer the alkyl groups due to the lack of competition in transfer hydrogenation. DHP **2a** bearing cyano groups was the only C4 dialkyl substituted DHP which could be obtained. However, the designed reaction didn't take place. Moreover, the corresponding C4 single benzyl substituted DHP

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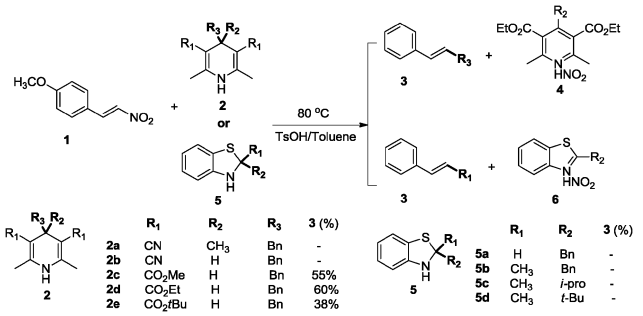


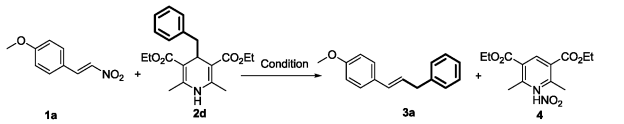
Scheme 2 Screening of alkyl donors for alkyl transfer.

2b couldn't transfer alkyl as well. Surprisingly, it was found that DHPs with ester substituents could transfer the benzyl group with high efficiency (Scheme 2, **2c–2e**). Even more interesting was the alkyl transfer product, which was exclusively *trans*-olefin. Moreover, we found that DHP **2d** with an ethyl ester substituent transferred the benzyl group more efficiently than the corresponding methyl ester substituted DHP **2c** and *tert*-butyl ester substituted DHP **2e**.

Meanwhile, alkyl substituted benzothiazoles, already applied for transfer alkylation of imines,[6] were synthesized and used in our alkyl transfer reaction. C-2 single benzyl substituted benzothiazole **5b** or disubstituted benzothiazoles **5b–5d**, were screened, however, the expected alkyl transfer reaction did not take place.

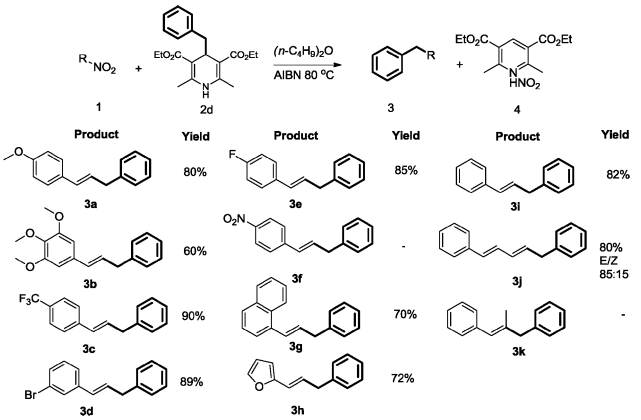
Next we turned our attention to ascertain the initial scope for this unexpected alkylation reaction. Reaction conditions were optimized by using **2d** as an alkyl transfer donor and nitro-olefin **1a** as the acceptor. It was found that the alkylation reaction could not take place at the low temperature of 60 °C (Table 1, entry 2). Considering that the reaction may proceed through a free radical mechanism, we used the radical initiator AIBN to promote the reaction at 60 °C without a Brønsted acid catalyst. To our delight, the alkylation reaction proceeded with higher efficiency compared with TsOH at 80 °C (Table 1, entry 3). Meanwhile, the radical scavenger TEMPO inhibited the alkylation reaction (Table 1, entry 4). Therefore, we speculated that the reaction may proceed through a radical

Table 1 Standardization of the alkyl transfer reaction conditions[a]



Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	TsOH 30%	Toluene	80	60
2	TsOH 30%	Toluene	60	—
3	AIBN 50%	Toluene	60	62
4	AIBN/TEMPO	Toluene	60	—
5	AIBN 1 eq.	Toluene	80	70
6	AIBN 1 eq.	AcOH	80	65
7	AIBN 1 eq.	*n*-Butyl ether	80	73
8[c]	AIBN 1 eq.	*n*-Butyl ether	80	80

[a] Reaction conditions: 1 eq. nitro-olefin **1a** (0.2 M in solvent), DHP **2d** (1.5 eq.), catalyst or additives were stirred in a nitrogen environment at the given temperature. [b] Yields are calculated after purification from silica column depending on **1a**. [c] The ratio of **1a**/**2d** is 1/2.



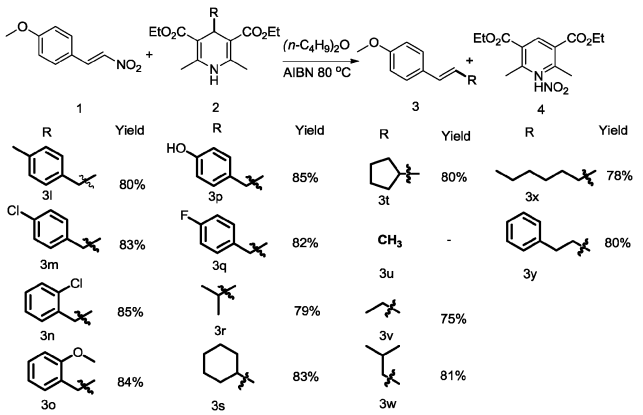
Scheme 3 Screening of nitro-olefins for alkyl transfer.

mechanism. Further screening of the appropriate reaction solvent revealed that *n*-butyl ether was better to use for higher alkyl transfer efficiency (Table 1, entries 5–7). Finally, the ratio of the reaction material was standardized and the optimal ratio for **1a**/**2d** was found to be 1/2 (Table 1, entry 8).

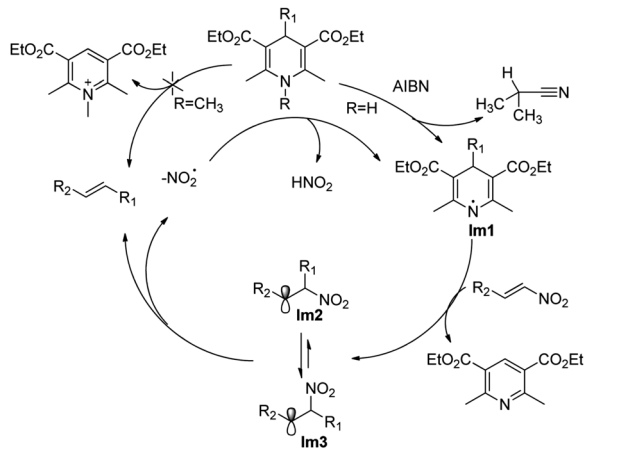
Further we explored the scope of the nitro-olefin acceptors in the alkyl-transfer reactions using benzyl substituted DHP **2d** as a representative donor (Scheme 3). Nitro-olefins bearing electron withdrawing groups or electron donating groups on the aromatic rings were readily used in the alkyl transfer reactions with high efficiency (**3a–3e**, **3g–3j**). *Trans*-olefins were obtained exclusively with up to 90% yield except for **3j** which was obtained as a mixture of the *trans*- and *cis*-olefins. Meanwhile, the results revealed that nitro-olefins with electron withdrawing groups could readily be use in the alkyl transfer reaction with higher efficiency compared to nitro-olefins with electron donating groups. However, nitro-olefins with a *p*-nitro group substituted on the phenyl ring could not form the alkyl transfer product **3f**, which was ascribed to inhibition of the nitro group.[10] Interestingly, trisubstituted olefin **3k** could not be prepared through the alkyl transfer reaction, which was attributed to its slightly higher steric hindrance.

The unexpectedly high efficiency of alkyl transfer with benzyl substituted DHPs drove us to determine whether other alkyls could efficiently be transferred as well. Firstly, we screened benzyl groups with different substituents. The results revealed that the substituents performed well, regardless of being either electron-withdrawing (Scheme 4, **3m**, **3n**, **3q**) or electron-donating (Scheme 4, **3l**, **3o**, **3p**), delivering the desired *E*-olefin in good isolated yields (most > 80%). We further determined that secondary alkyl groups, whether open-chain (Scheme 4, **3r**) or cyclic (Scheme 4, **3s–3t**) could transfer with high efficiency. Finally, we screened primary alkyl groups, which were unable to transfer in our previous work.[6] The results revealed that all of the primary alkyl groups could transfer efficiently, except the methyl group which was ascribed to the transience of the methyl radical (Scheme 4, **3u–3y**).

Previous discussion about the mechanism of the transfer alkylation of imines with C-4 substituted DHPs focused on the two step concerted alkyl transfer process.[6] However, we propose here that the C-4 substituted DHPs could replace the nitro groups of the nitro-olefins with alkyl groups *via* a single



Scheme 4 Screening of the DHP donors for alkyl transfer.



Scheme 5 Proposed reaction mechanism.

electron transfer chain process (Scheme 5). Firstly, the free radical initiator AIBN decomposes to form 2-cyanoprop-2-yl radicals, which then initiate the alkyl transfer reaction. Then the DHP radical (Scheme 5, **Im1**) forms by extracting a hydrogen radical. The resultant DHP radical transfers the alkyl radical and adds to the nitro olefin due to the aromatization of the DHP ring. The resulting radical interconverts by internal rotation (Scheme 5, **Im2** and **Im3**), and then produces the thermodynamically controlled product – the *trans*-olefin – *via* β-elimination. Finally the resulting nitro radical will initiate further reaction cycles.

The reported results support this novel mechanistic assignment: (1) the alkylation reaction could be initiated with AIBN and quenched with TEMPO; (2) the alkylation product **3f** could not be prepared due to the presence of a *p*-nitro group; (3) special DHPs with *N*-methyl substitutents were intentionally prepared and used in the alkyl transfer reaction (R = CH_3, Scheme 5). However, we did not find the alkylation product but the unreacted DHP, which once again verified the mechanism.

In conclusion, we demonstrated an efficient alkyl transfer reaction which allows the formation of C–C bonds through C–C bond cleavage. The reasonable free radical reaction mechanism is different from the previous concerted reaction process. Meanwhile, the reaction conditions are mild and have been able to site selectively and stereoselectively prepare a range of *trans*-olefins. The scope of the transferred alkyls included benzyls, secondary alkyls and especially primary alkyls which were unable to transfer in our previous work. This study paves the way for the use of alkyl substituted Hantzsch esters to provide alkyl radicals, which are traditionally produced by splitting of C–X bonds rather than C–C bond cleavage. Further alkyl transfer experiments, as well as investigations into the reaction mechanisms, are underway in our lab.

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