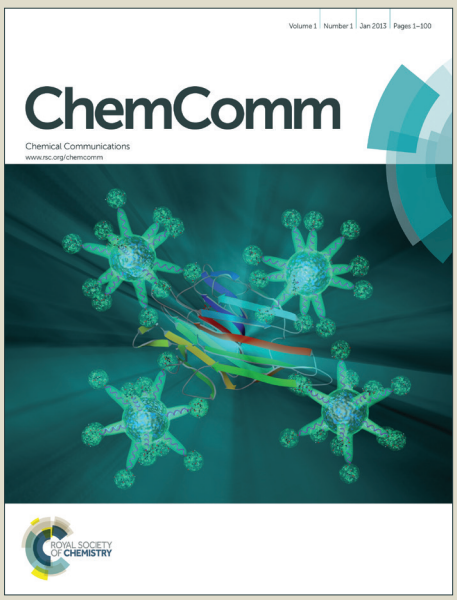
# ChemComm

Accepted Manuscript





ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

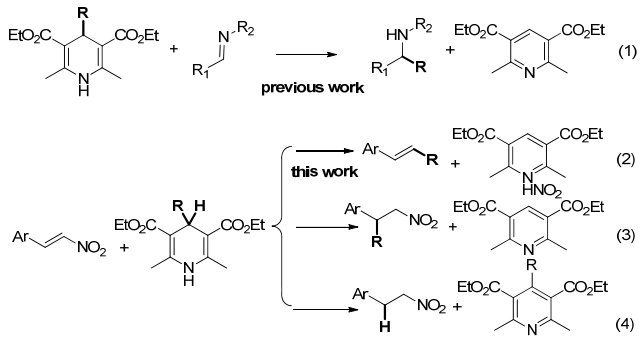
# Alkyl Transfer from C-C Cleavage: ReplaceNitro Group of Nitro-olefin

**Guangxun Li[a], Lei Wu[a], Gang Lv[a],Hongxin, Liu[a], Qingquan Fu[a], Xiaomei Zhang[b]and Zhuo Tang[a]***

***Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***
**DOI: 10.1039/b000000x**

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

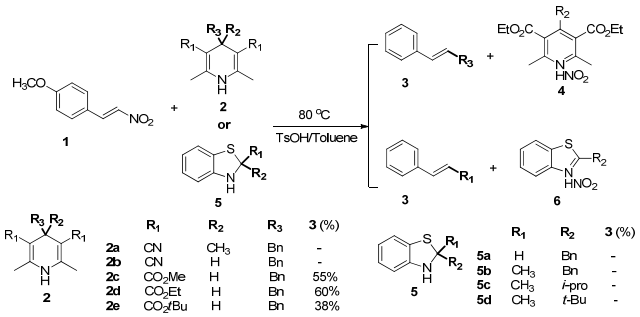
Methods for C-C bonds formation are basic toolbox for synthetic chemists. In spite of the myriad methods available,[1] an alternative metal free green chemistry route for C-C bonds formation, in terms of the operational simplicity and functional-group tolerance is in constant demand.[2]The highly efficient natural biochemical pathways to produce complex molecules is 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]




**Scheme 1** Alkyl transfer with alkyl substituted DHPs.

Hantzsch esters (HEH) are bio-inspired hydride donors, commonly known as synthetic analogues of reduced nicotinamide adenine dinucleotide (NADH). Taking advantage of the special hydrogen transfer property, a broad range of transfer hydrogenations are conducted.[5] However, the study of alkyl transfer in this way have never been addressed until the recent work by our group.[6] Similar to the corresponding transfer hydrogenation, high efficiency C-4 alkyl substituted DHPs were rationally designed for alkylation of imines (Scheme. 1, equation 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 gave 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, equation 2). In fact, 1,4-cyclohexadienederivatives has 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 bond 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, equation 3). Apparently, this alkyl transfer reaction was difficult to anticipate for the following reasons: 1) the competitive hydrogen transfer reaction (Scheme. 1, equation 4), 2) the transfer mechanism was unknown which may proceed through concerted process[9] or free radical process.[10] For example, DHP analogue 1-benzyl-1, 4-dihydronicotinamide (BNAH) was used as a reagent for replacing aliphatic nitro group by hydrogen through 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]

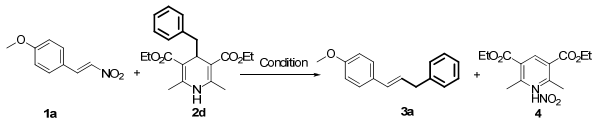



**Scheme 2** Screening of the alkyl donors for alkyl transfer.

Our study of the alkyl transfer started with the hypothesis that DHPs with two alkyls 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 dialkyls substituted DHP which could be obtained. However, the designed reaction didn't take place. Moreover, the corresponding C4 single benzyl substituted DHP **2b** couldn't transfer alkyl as well. Surprisingly, it was found that DHPs with esters substituted 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 ethyl ester substituted transferred the benzyl group more efficiently than the corresponding methyl esters substituted DHP **2c** and *tert*-butyl esters 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 could not take place.

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

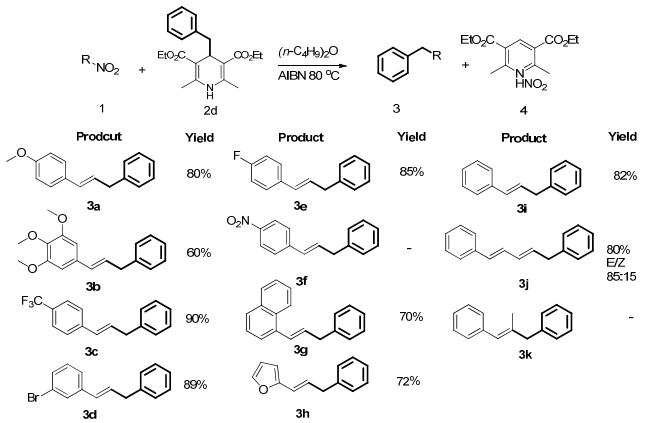



| Entry | Catalyst | Solvent | T ℃ | Yield[b]% |
|---|---|---|---|---|
| 1 | TsOH 30% | Toluene | 80 | 60 |
| 2 | TsOH 30% | Toluene | 60 | - |
| 3 | AIBN 50% | Toluene | 60 | 62 |
| 4 | AIBN/TEMPO | Toluene | 60 | - |
| 5 | AIBN 1eq. | Toluene | 80 | 70 |
| 6 | AIBN 1eq. | AcOH | 80 | 65 |
| 7 | AIBN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

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

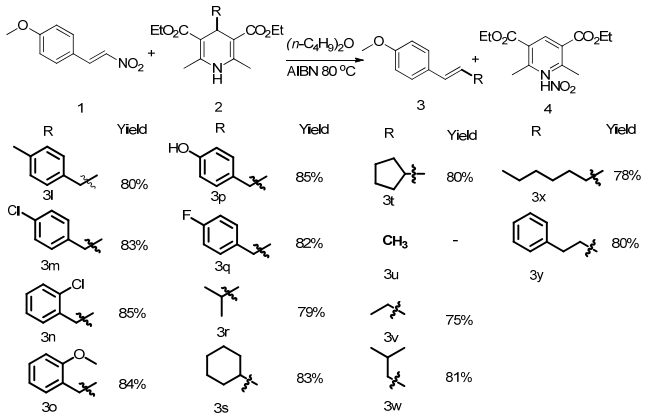
Next we turned our attention to ascertain an initial scope for this unexpected alkylation reaction. Reaction conditions were optimized by using **2d** as alkyl transfer donor and nitro-olefin **1a** as acceptor. It was found that alkylation reaction could not take place at low temperature of 60℃ (Table 1, entry 2). Considering that the reaction may proceed through free radical mechanism, we used radical initiator AIBN to promote the reaction at 60℃ without brønsted acid catalyst. To our delight, the alkylation reaction has proceeded with higher efficiency compared with TsOH at 80℃ (Table 1, entry 3). Meanwhile, radical scavenger TEMPO inhibited the alkylation reaction (Table 1, entry 4). Therefore, we speculated that the reaction may proceed through radical 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 be1/2 (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 *trans*- and *cis*-olefin. Meanwhile, the results revealed that nitro-olefins with electron withdrawing groups could readily use in the alkyl transfer reaction with higher efficiency compared with nitro-olefins with electron donating groups. However, nitro-olefin with *p*-nitro group substituted on the phenyl ring could not get the alkyl transfer product **3f**, which was ascribed to the inhibition of the nitro group.[10] Interestingly, tri-substituted olefin **3k** could not be prepared through the alkyl transfer reaction, which was attributed to the slightly higher steric hindrance.




**Scheme 3** Screening of nitro-olefins for alkyl transfer.

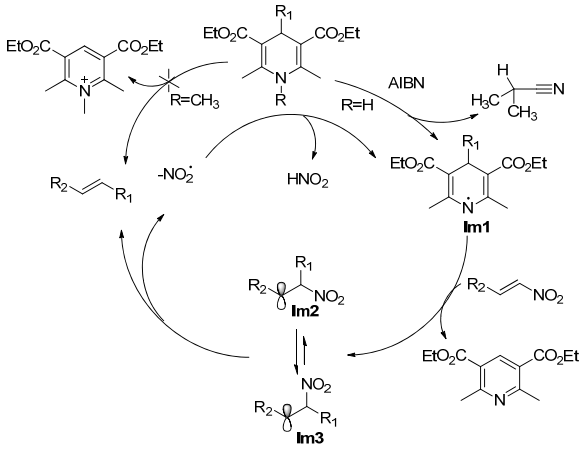
The unexpected high efficiency of alkyl transfer with benzyl substituted DHPs drove us to determine whether other alkyls could efficiently transfer as well. Firstly, we screened the benzyl groups with different substituents. The results revealed that the substituents regardless of either electron-withdrawing (Scheme. 4, **3m**, **3n**, **3q**) or electron-donating (Scheme.4, **3l**, **3o**, **3p**) performed well, delivering the desired *E*-olefin in good isolated yields (most>80%). We further examined that the 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 methyl group which was imputed to the transient of methyl radical(Scheme. 4, **3v**-**3y**).




**Scheme 4** Screening of the DHP donors for alkyl transfer.

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 proposed here that the C-4 substituted DHPs could replace the nitro groups of the nitro olefins by alkyl groups via single electron transfer chain process (Scheme. 5). Firstly, the free radical initiator AIBN decomposes to form 2-cyanoprop-2-yl radicals, which then initiated the alkyl transfer reaction. Then the DHP radical

(Scheme. 5, **Im1**) formed by extracting hydrogen radical. The resulted DHP radical transfered the alkyl radical and added to the nitro olefin due to the aromatization of the DHP ring. The resulted radical interconverted by internal rotation (Scheme. **Im2** and **Im3**), and then produced thermodynamically controlled product-the *trans*-olefin via *β*-elimination. Finally the resulted nitro radical will initiate the further reaction cycles.




**Scheme 5** Proposed reaction mechanism.

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 *p*-nitro group; 3) Special DHPs with N-methyl substituted was 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 bond 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 paved the way for the use of alkyl substituted Hantzsch ester to provide alkyl radical, which was traditionally produced by splitting of C-X bond rather than C-C bond cleavage. Further alkyl transfer experiments, as well as the reaction mechanisms are underway in our lab.

## Acknowledgements

We are grateful for the financial support from Chinese Academy of Science (Hundreds of Talents Program) and National Sciences Foundation of China (Grant No. 21102139) and Innovation Program of the Chinese Academy of Sciences (Grant No. KSCX2-EW-J-22).

## Notes and references

[a] Natural Products Research Center Chengdu Institution of Biology Chinese Academy of Science Chendu Sichuan 610041(China) E-mail:tangzhuo@cib.ac.cn

[b]Chengdu Institute of Organic Chemistry Chinese Academy of Sciences Chendu Sichuan 610041(China)

† Electronic Supplementary Information (ESI) available: Experimental procedures include the synthetic protocol of the alkyl transfer reaction as well as full spectroscopy data of the related products. See DOI:10.1039/b000000x/

1. (*a*)G. S. Silverman, P. E. Rakita, *Handbook of Grignard Reagents*,Marcel Dekker, New York, 1996; (*b*)*Modern Aldol Reactions*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2008; (*c*) S. Stevelmans, *Michael Reaction Kinetics and Process Design*, Stan Ackermans Instituut, 1997;(*d*)I. J. S. Fairlamb, J. M. Lynam, *Organometallic Chemistry, Vol. 34*, 2008.
2. J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nature chem.* 2009, **1**, 494-499.
3. *(a)*P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed., John Wiley & Sons, Chichester, **2011**; *(b)*S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* 2011, **475**, 183-188.
4. *(a)* D. Enders, M. R. M. Hüttl, O. Niemeier, M. T. Reetz, B. List, S. Jaroch, H. Weinmann*, Vol. 2007/2*, Springer Berlin Heidelberg, New York, **2008**, pp.145-157; *(b)* Y. Pan, C.-H. Tan, *Synthesis*, 2011, 2044-2053.
5. For recent reviews on asymmetric reactions using Hantzschesters, see:*(a)*H. Adolfsson, *Angew. Chem. Int. Ed.* 2005, **44**, 3340-3342; *(b)* Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc.Chem. Res.* 2007, **40**, 1327-1339. *(c)* You, S. L. *Chem. Asian J.* 2007, **2**, 820-827.*(d)* Connon, S. J. *Org. Biomol. Chem.* 2007, **5**, 3407-3417. *(e)* Rueping, M.;Dufour, J.; Schoepke, F. R. *Green Chem.* 2011, **13**, 1084-1105.*(f)* J. G. de Vries, N. Mrsic, *Catal. Sci. Technol.* 2011, **1**, 727-735; (*g*) C. Zheng, S.-L. You, *Chem. Soc. Rev.* 2012, **41**, 2498-2518.
6. G. Li, R. Chen, L. Wu, Q. Fu, X. Zhang, Z. Tang, *Angew. Chem. Int. Ed.* 2013, **52**, 8432-8436.
7. (*a*)Walton, J. C.; Studer, A. *Acc. Chem Res*2005, **38**, 794-802; (*b*) A. Studer, S. Amrein, *Angew. Chem. Int. Ed.* 2000, **39**, 3080-3082; (*c*) A. Studer, S. Amrein, F. Schleth, T. Schulte, J. C. Walton, *J. Am. Chem. Soc.* 2003, **125**, 5726-5733;(*d*)J. Guin, C. Mück-Lichtenfeld, S. Grimme, A. Studer, *J. Am. Chem. Soc.* 2007, **129**, 4498-4503; (*e*)J. Kemper, A. Studer, *Angew. Chem. Int. Ed.* 2005, **44**, 4914-4917; (*f*)J. Guin, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* 2008, **47**, 779-782; (*g*)L. V. Jackson, J. C. Walton, *J. Chem. Soc., Perkin Trans. 2,*2001, 1758-1764; (*h*)C.-M. Chou, J. Guin, C. Mück-Lichtenfeld, S. Grimme, A. Studer, Chem.AsianJ., 2011,**6**, 1197-1209; (*i*)P. A. Baguley, L. V. Jackson, J. C. Walton, *J. Chem. Soc. Perkin Trans. 1*. 2002, 304-309.
8. (*a*) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* 2007, **129**, 8976-8977; (*b*) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* 2008, **130**, 13862-13863.
9. X.-Y. Liu, C.-M. Che, *Org. Lett.* 2009, **11**, 4204-4207.
10. N. Ono, R. Tamura, A. Kaji, *J. Am. Chem. Soc.* 1983, **105**, 4017-4022.
11. (*a*) C.-F. Yao, C.-M. Chu, J.-T. Liu, *J. Org. Chem.* 1998, **63**, 719-722; (*b*) J.-T. Liu, Y.-J. Jang, Y.-K. Shih, S.-R. Hu, C.-M. Chu, C.-F. Yao, *J. Org. Chem.* 2001, **66**, 6021-6028; (*c*) C.-M. Chu, J.-T. Liu, W.-W. Lin, C.-F. Yao, *J. Chem. Soc. Perkin Trans. 1*. 1999, **1999**, 47-52; (*d*) J.-Y. Liu, J.-T. Liu, C.-F. Yao, *Tetrahedron Lett.* 2001, **42**, 3613-3615; (*e*)J.-Y. Liu, Y.-J. Jang, W.-W. Lin, J.-T. Liu, C.-F. Yao, *J. Org. Chem.* 2003, **68**, 4030-4038; (*f*)Y.-J. Jang, Y.-K. Shih, J.-Y. Liu, W.-Y. Kuo, C.-F. Yao, *Chem.-Eur. J.* 2003, **9**, 2123-2128.