Alkylation

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Alkyl Transfer from C–C Cleavage**

*Guangxun Li, Rong Chen, Lei Wu, Qingquan Fu, Xiaomei Zhang, and Zhuo Tang**

Modern organic synthesis requires the development of efficient methods for the construction of complex molecules, and C–C bond formation continues to be key to methodological advancement. In spite of the myriad methods available,[1] advantageous methodologies in terms of the availability of starting materials, operational simplicity, functional-group tolerance, and the absence of metals are in constant demand.[2] The beauty and diversity of the biochemical pathways developed by nature 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 provides insight into possibilities for similar transformations by chemical synthesis. In this way, chemists have designed many biomimetic organocatalytic C–C bond-forming reactions.[4] Herein we report a mild, metal-free, operationally simple strategy for the formation of C–C bonds by alkyl transfer through C–C bond cleavage. We demonstrate the broad utility of this strategy based on the use of Hantzsch ester (HEH) analogues as alkyl donors and imines as acceptors. The transfer of alkyl groups bearing hydroxy, ether, and ester substituents occurred with high efficiency.

HEHs are biologically inspired hydride donors that are commonly known as synthetic analogues of reduced nicotinamide adenine dinucleotide (NADH). Their potential as a hydrogen source was acknowledged for the first time in 1955 by Mauzerall and Westheimer, who showed that HEHs can reduce carbonyl compounds by direct hydrogen transfer to the substrate.[5] Since then, a broad range of transfer-hydrogenation reactions conducted with HEHs in combination with different catalysts and additives have been reported [Eq. (1)].[6] Considerable effort has been directed towards the design of effective HEH reagents that operate in conjunction with different catalysts for asymmetric transfer hydrogenation;[7] however, alkyl transfer in this way has never been investigated and poses a distinct and formidable challenge. The development of such a transfer alkylation could be hindered by 1) competitive hydrogen transfer and 2) the lack of knowledge about the mechanism of hydrogen transfer, which could involve hydride (H^-) transfer, the transfer of a hydrogen radical ($H^\bullet$), or a concerted process.[7] However, there are a great deal of examples of dealkylation at the 4-position of the pyridine ring during the oxidation of dihydropyridine derivatives (DHPs) with numerous oxidizing reagents.[8] Furthermore, the use of Hantzsch esters as a potential method for alkyl transfer would benefit from the advantages of these reagents over organometallic reagents in terms of their stability, availability, and low toxicity.[9] A transfer hydrogenative C–C coupling enables addition to carbonyl groups without the need for preformed organometallic reagents; however, the reaction is restricted to limited substrates.[10]

$$\text{Hydrogen transfer} \quad DH_2 + A \overset{\text{cat.}}{\rightleftharpoons} D + AH_2 \tag{1}$$

$$\text{Alkyl transfer} \quad R{-}DH + A \overset{\text{cat.}}{\rightleftharpoons} D + R{-}AH \tag{2}$$

D = donor; A = acceptor

Intrigued by these challenges and advantages, we pursued a significant and unprecedented C–C bond-forming reaction by alkyl transfer. This synthetic method offers not only the advantage of convenience, but also a strategic divergence from traditional approaches. Herein, we define this significant reaction as an "alkyl transfer" or "transfer alkylation" owing to the innate character of the reaction: the transfer of an alkyl group from an organic donor molecule to an organic acceptor through carbon–carbon bond cleavage [Eq. (2)]. Although Sai et al. reported a similar alkyl transfer promoted by an N-heterocyclic carbene/copper complex, the reaction was limited to the transfer of allyl, allenyl, and propargyl groups.[11] To our knowledge, there is only one example of such a process in nature: The weakly basic histidine motif of polyketide synthase (PKS) activates the malonic acid half-thioester (MAHT) toward decarboxylation, and the resulting thioester enolate undergoes electrophilic trapping with an acyl unit to furnish the Claisen condensation product.[12] However, the essence of this reaction is transfer acylation, which in fact finally gives an adol,[13] Mannich,[14] or Michael[15] product.

Our study of the alkyl-transfer reaction started with the hypothesis that DHPs with two alkyl substituents at the C4 position should only transfer the alkyl group without the competition of transfer hydrogenation. DHP **1a** bearing cyano groups was the only C4-disubstituted DHP that we could obtain. However, the designed reaction did not take place (Table 1, entry 1). In contrast, the transfer of hydrogen proceeded effectively when DHP **1b** with one alkyl substituent was used in the same reaction (Table 1, entry 2). We speculated that the benzyl group was too big to compete with

[*] G.-X. Li, R. Chen, L. Wu, Q. Fu, Prof. Dr. Z. Tang
Natural Products Research Center, Chengdu Institute of Biology
Chinese Academy of Sciences
Chendu Sichuan 610041 (China)
E-mail: tangzhuo@cib.ac.cn
G.-X. Li, Prof. Dr. X.-M. Zhang
Chengdu Institute of Organic Chemistry
Chinese Academy of Sciences
Chendu Sichuan 610041 (China)

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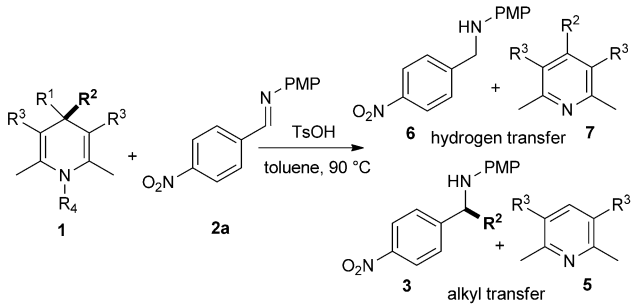
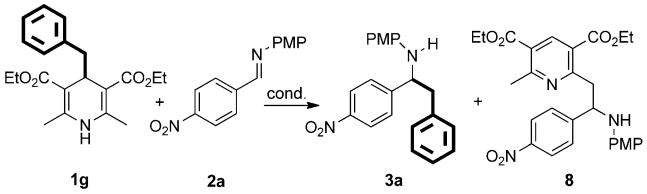
Table 1: Development of a method for C–C bond formation on the basis of alkyl transfer.[a]



Entry	DHP	R^1	R^2	R^3	R^4	Yield [%][b] 6	3
1	**1a**	Me	Bn	CN	H	–	
2	**1b**	H	Bn	CN	H	80	
3	**1c**	H	Me	CO_2Me	H	82	
4	**1d**	H	Me	CO_2Et	H	80	
5	**1e**	H	Me	CO_2tBu	H	40	
6	**1f**	H	Bn	CO_2Me	H	20	30
7	**1g**	H	Bn	CO_2Et	H	10	50
8	**1h**	H	Bn	CO_2tBu	H	10	20
9	**1i**	H	Bn	CO_2Et	Me	10	45

[a] Reaction conditions: imine **2a** (0.2 M in toluene, 1 equiv), alkyl-transfer donor **1** (1.2 equiv), TsOH (0.3 equiv). [b] Yield of the isolated product. Bn = benzyl, PMP = *p*-methoxyphenyl, Ts = *p*-toluenesulfonyl.

Table 2: Influence of the catalyst and reaction conditions on the alkyl-transfer reaction.[a]



Entry	*T* [°C]	Catalyst	Yield [%][b] 3a	8
1	RT	TsOH	8	42
2	50	TsOH	20	20
3[c]	90	TsOH	50	< 5
4[d]	RT	TsOH	–	60
5[c,d]	90	TsOH	–	65
6	RT	$AlCl_3$	30	20
7	RT	$GaCl_3$	30	10
8	RT	$InCl_3$	40	9
9	RT	$BF_3{\cdot}Et_2O$	57	3
10	40	$BF_3{\cdot}Et_2O$	67	2
11[e]	50	$BF_3{\cdot}Et_2O$	80	< 1

[a] Reaction conditions: imine **2a** (0.2 M in chloroform, 1 equiv), alkyl-transfer donor **1** (1.2 equiv), catalyst (30 mol)%. [b] Yield of the isolated product. [c] Toluene was used as the solvent. [d] Compound **5a** was used instead of **1g** as the DHP substrate. [e] The reaction was carried out with 1.2 equivalents of $BF_3{\cdot}Et_2O$.

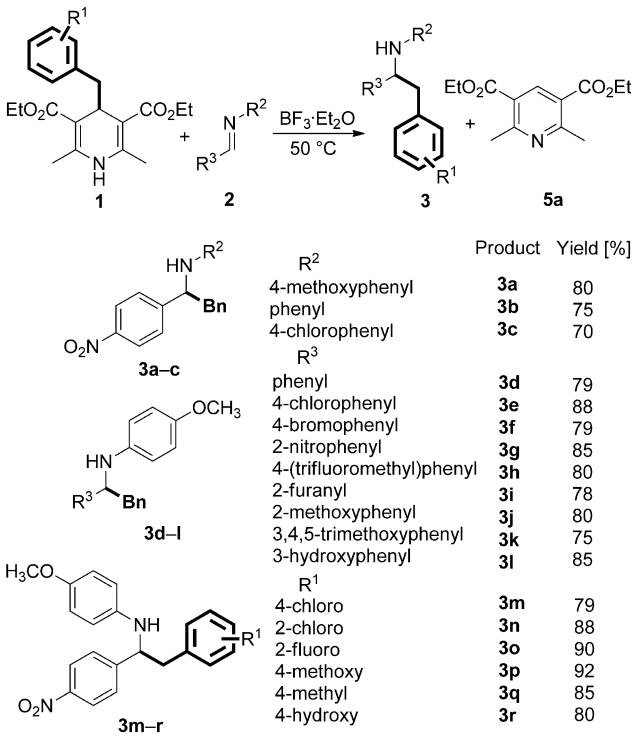
the hydrogen atom. Therefore, we screened C4-methyl-substituted DHPs **1c**–**1e** with different ester groups from the point of view of steric hindrance and found that the reaction proceeded with hydrogen transfer only (Table 1, entries 3–5). Encouragingly, when we exchanged the methyl substituent for a benzyl group, the desired reaction occurred, despite a little concomitant transfer hydrogenation (Table 1, entry 6). We investigated the reaction of DHPs with different ester substituents and found that the corresponding DHP with an ethyl ester group was most effective (Table 1, entries 7 and 8). Further study revealed that DHP **1i** with an *N*-methyl substituent was also suitable for the alkyl transfer, despite a slightly lower alkyl-transfer efficiency (Table 1, entry 9).

To ascertain the initial scope of the reaction, we optimized the reaction conditions by using **1g** as the alkyl-transfer donor and imine **2a** as the acceptor (Table 2). When we decreased the reaction temperature, we found that the expected alkyl transfer became inefficient, and an unexpected product **8** appeared (Table 2, entries 1–3). We assumed that a side reaction may proceed between imine **2a** and side product **5a** according to the previously reported mechanism,[16] and this hypothesis was supported by reactions of the dealkylation product **5a** as a substrate with imine **2a** (Table 2, entries 4 and 5). To further improve the alkyl-transfer efficiency, we screened a range of Lewis acid catalysts (Table 2, entries 6–9). Of all the Lewis acids tested, $BF_3{\cdot}Et_2O$ turned out to be the most efficient catalyst and most capable of minimizing the side reaction. By optimizing the reaction conditions, we developed a standard experimental protocol for the novel alkyl-transfer reaction: The alkyl-transfer donor **1** (1.2 equiv) was stirred with the imine acceptor **2** (1.0 equiv) and $BF_3{\cdot}Et_2O$ (1.2 equiv) in chloroform at 50 °C for 2 days. Under the optimized conditions, alkylation product **3a** was obtained as the sole product in 80 % yield.

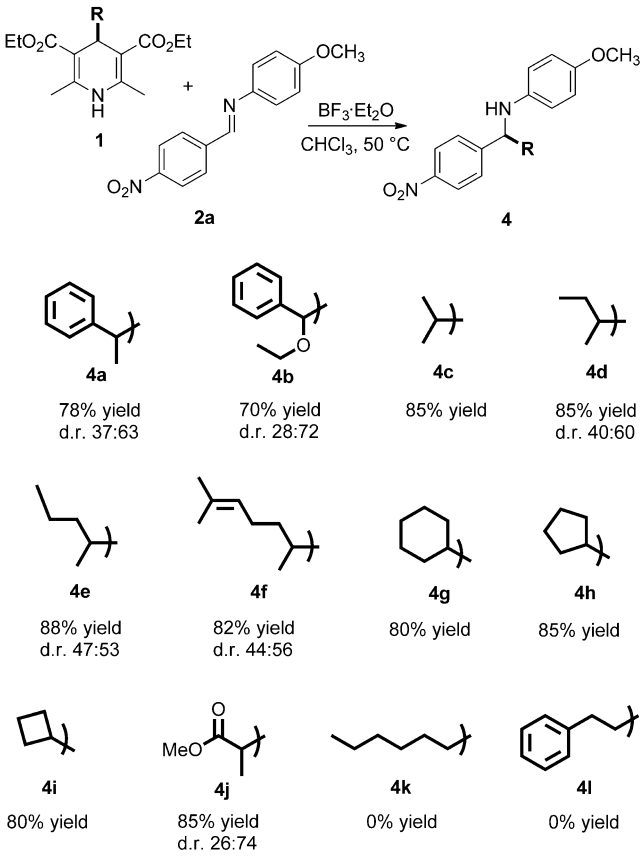
We then evaluated the scope of the alkyl-transfer process in terms of the imine acceptor by using the benzyl-substituted DHP **1g** as a representative donor (Scheme 1). Imine acceptors bearing an electron-withdrawing group or an electron-donating group on the aniline ring readily underwent the alkyl-transfer reaction with high efficiency (products **3a**–**c**). We were also delighted to observe that imines formed from aldehydes bearing electron-withdrawing groups or electron-donating groups were transformed into the desired products **3e**–**h** and **3i**–**l**, respectively, with high alkyl-transfer efficiency.

The DHP component was similarly examined with different benzyl substituents in the reaction with imine **2a** (Scheme 1, products **3m**–**r**). We found that the transformation proceeded well regardless of whether the benzyl ring was substituted with electron-withdrawing or electron-donating groups and isolated the desired amines in good yield (mostly > 80 %). Particular attention was paid to common functional groups that might cause difficulties in amine preparation with the relevant Grignard reagent (Scheme 1, products **3m**,**n**). However, the alkyl-transfer efficiency was unaffected. Furthermore, an unprotected DHP bearing a hydroxy-substituted benzyl group was converted into the corresponding amine **3r** in 80 % yield (Scheme 1).

The unexpected high efficiency of alkyl transfer with benzyl-substituted DHPs prompted us to investigate whether DHPs with simple alkyl substituents could also efficiently transfer the alkyl group. At the beginning of our research, we found that a methyl group could not be transferred in the reaction (Table 1, entries 3–5). Further studies revealed that



Scheme 1. Bioinspired benzyl transfer with DHPs.

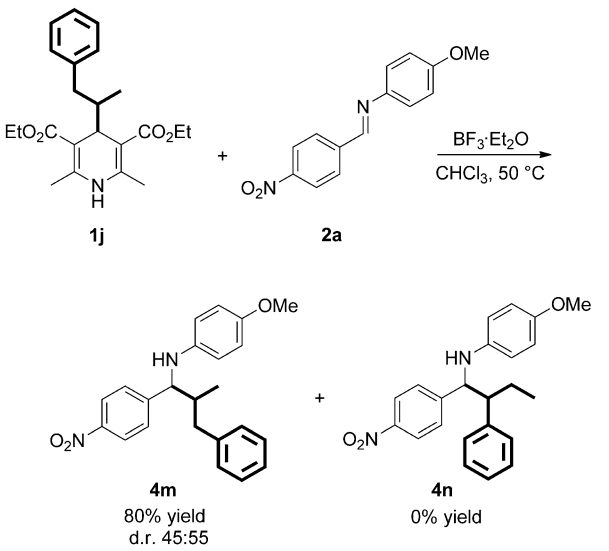


Scheme 2. Bioinspired alkyl transfer with DHPs.

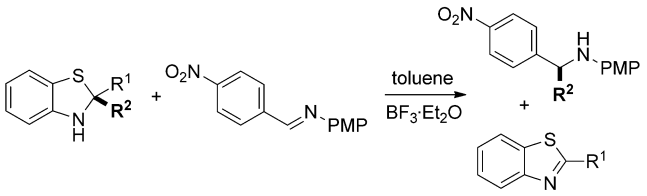
ethyl and propyl groups could also not be transferred (data not shown). However, when DHPs substituted with secondary alkyl groups were used as substrates, high efficiency of alkyl transfer was observed (Scheme 2, mostly $>80\,\%$). We examined substituents attached at the benzylic position and found that alkyl-substituted and even alkoxy-substituted DHPs performed well, although the products were formed with a low diastereomeric ratio (Scheme 2, products **4a**,**b**). To our knowledge, this alkylation is impossible with the corresponding organometallic reagents. Secondary alkyl groups, whether open-chain (Scheme 2, products **4c**–**f**) or cyclic (Scheme 2, products **4g**–**i**), short-chain (Scheme 2, products **4c**,**d**) or long-chain (Scheme 2, products **4e**,**f**), small-ring (Scheme 2, product **4i**) or large-ring substituents (Scheme 2, product **4g**), could be transferred with high efficiency. Furthermore, an ester-substituted DHP efficiently provided the Mannich-type product **4j**, which could not be formed easily in a traditional Mannich reaction owing to the low acidity of the α hydrogen atom (Scheme 2).[17] To ascertain if other primary alkyl groups can be transferred, we screened several DHPs with typical alkyl substituents, such as a DHP substituted with a long alkyl chain and the corresponding phenethyl-substituted DHP. However, none of these DHPs transferred the alkyl group in the model reaction; instead, hydrogen was transferred (Scheme 2, products **4k**,**l**). We inferred from the above experimental results that the alkyl-transfer reaction may proceed through a free-radical mechanism.

We next turned our attention to the elucidation of the reaction mechanism and carried out a series of experiments (see the Supporting Information). In one experiment, we added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical scavenger to the reaction mixture and found that the reaction still proceeded well without loss of yield. In another experiment, the addition of azobisisobutyronitrile (AIBN) to the reaction mixture without the catalyst did not afford any product even after 3 days. Furthermore, we found that the alkyl-transfer reaction was insusceptible to light. On the other hand, when DHP **1j** with a 1-phenylpropan-2-yl substituent was used as the substrate in our reaction, only one alkyl-transfer product was obtained (Scheme 3, product **4m**). If the alkyl-transfer reaction proceeded through a radical process, the reaction of **1u** could also afford the rearrangement product **4n**, which was not observed. On the basis of these experiments, we excluded the possibility of a radical mechanism. Moreover, we could also rule out the possibility that the alkyl group was transferred to imine **2a** as a free carbanion, since the alkyl-transfer reaction was immune to an excess amount of a Brønsted acid catalyst (see the Supporting Information). Therefore, we propose that the alkyl-transfer reaction may proceed through a concerted process in analogy with the similar transfer-hydrogenation process;[9] thus, the DHP may transfer the alkyl functional group directly to the imine in a concerted way (see the Supporting Information).

To verify this mechanism, we designed a chiral DHP substituted with a chiral alkyl group as an alkyl-transfer substrate (see Figure S2 in the Supporting Information). We thought that the transfer group would be able to transfer its chirality to the product if the reaction proceeded by a concerted mechanism. However, the products turned out



Scheme 3. Alkyl-transfer reaction with a 4-(1-phenylpropan-2-yl)-substituted DHP substrate.



R^1	R^2	T [°C]	Product	Yield [%]
H	Bn	90	**3a**	75
H	*i*Pr	90	**4c**	80
Me	*t*Bu	60	**4o**	85

Scheme 4. Bioinspired alkyl transfer with benzothiazoles.

to be racemic. Moreover, the diastereomeric ratio of the product was identical to that of the alkylation product formed with the corresponding racemic DHP (see Figure S3). Another chiral DHP characterized by the presence of bulky chiral ester groups was also used as an alkyl-transfer substrate (see Figure S2), as we hypothesized that the steric bulk of the chiral ester groups might induce chirality in the alkyl-transfer product. However, this product was also racemic (see Figure S3). Furthermore, a chiral Lewis acid and Brønsted acid were used as catalysts for asymmetric alkyl transfer (see the Supporting Information). However, the alkyl-transfer product was racemic, although a chiral sulfonic acid could catalyze the reaction in moderate yield. Therefore, in our alkyl-transfer reaction, a process involving simultaneous C–C cleavage and C–C formation is unreasonable. We thus inferred that the alkyl transfer may proceed through a practically concerted mechanism in which C–C bond cleavage occurs to provide a carbanion that undergoes nearly instantaneous addition to the imine.

Benzothiazole was another type of biologically inspired hydrogen-transfer donor that had been used successfully for the hydrogenation of imines.[18] Therefore, we hoped that our alkyl-transfer reaction would also take place with benzothiazole substrates. As we had imagined, the designed alkyl transfer proceeded smoothly in the synthesis of amines with high yield (Scheme 4, products **3a** and **4c**). Furthermore, a tertiary carbon substituent was transferred with high efficiency, which was not possible with the corresponding DHP (Scheme 4, product **4o**).

In this study, we have demonstrated a nonconventional C–C bond-forming method that enables the facile synthesis of amines. The conditions are mild and have been shown to accommodate a range of imines. Unlike known alkylation reactions in which the alkyl group is obtained through the cleavage of either a carbon–metal or carbon–halide bond, this novel reaction involves catalytic C–C cleavage and transfer of the desired alkyl group to an organic acceptor. We screened the transfer capacity of DHP substrates thoroughly and found that benzyl groups and secondary alkyl substituents can be transferred efficiently, whereas primary alkyl and olefinic groups can not be transferred. At the levels of strategy and mechanism, this alkyl transfer reaction appears to proceed through an indirect concerted process. Factors that affect the transfer process include electronic effects and aromatization tendency. In all, this strategic shift may ultimately become a practical and complementary alternative to organometallic processes. It also overturns more than half a century of received wisdom regarding the reactivity of HEHs in hydrogen transfer. We hope that our preliminary investigation will attract great attention to the field of carbon-substituent transfer and broaden the scope of bioinspired synthesis.

Experimental Section

The DHP (0.13 mmol, 1.3 equiv), the imine (0.1 mmol, 1.0 equiv), $BF_3{\cdot}Et_2O$ (1.2 equiv), and chloroform (1 mL) were placed in a reaction tube, and the mixture was heated at 50 °C with stirring under a nitrogen atmosphere. When the reaction was complete (as shown by TLC), the crude reaction mixture was allowed to reach room temperature, the solvent was evaporated, and a 3 N solution of aqueous hydrochloride acid and dichloromethane were added. The aqueous and organic layers were separated, and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed twice with water, then with brine, and were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by chromatography on silica gel.

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