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Isocyanide-Based Multicomponent Reactions: Concise Synthesis of Spirocyclic Oxindoles with Molecular Complexity by Using a [1,5]-Hydrogen Shift as the Key Step

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Abstract: A concise multicomponent reaction of isocyanide, α-substituted allenoate, and methyleneindolinone has been disclosed. This protocol provides a fast and straightforward approach to synthesize unusual tricyclic oxindoles in an efficient and atom-economic manner. Mechanistically, the present cycloaddition may proceed through a cascade sequence involving double Michael addition, double cyclization, double [1,5]-hydrogen shift, and group migration. The introduction of a special alkyl group to the allenoate is believed to play a key role in the cascade reaction. This method also features a broad substrate scope, which is particularly useful for the delivery of a large number of compounds.

As valuable C1 synthons, isocyanides have proven themselves to be irreplaceable building blocks in organic synthesis.[1] The past decades have witnessed a rapid increase in various carbon–carbon and carbon–heteroatom bond-forming reactions involving isocyanides.[2,3] Remarkably, the exceptional divalent carbon atoms of isocyanides[4] makes them particularly versatile components in multicomponent reactions (MCRs).[5] It is therefore not surprising that the isocyanide-based multicomponent reactions (IMCRs) have enjoyed considerable attention from the synthetic community because of good atom- and step-economy, convergence, and increased structural complexity.[6] Moreover, IMCRs hold great promise for the fast and efficient generation of complex and diverse druglike small molecules, which would be superior to traditional methods. Since most of the MCRs were found on the basis of bimolecular reactions, concise combination of reactive isocyanide functional groups with known reactions is of fundamental importance.[7]

In 2011, we reported the first example of a multicomponent reaction involving an isocyanide and allenoate.[8a] Since then, we have spent much time in exploring the potential synthetic utility of the isocyanide-based [2+2+1] three-component reactions with allenoate, thus providing a quick access to the syntheses of functionalized carbocycles and natural-product-like N-containing heterocycles.[8b,c] Mechanistically, the above-mentioned three-component reaction is closely related to famous phosphine-catalyzed cycloaddition with allenoate (Scheme 1). The history of phosphine-catalyzed [3+2] reactions can be dated back to 1995 when Lu and co-workers disclosed their pioneering work on the phosphine-catalyzed cycloaddition of allenoates and alkenes.[9] So far, the chemistry of organophosphine catalysis has been well documented and has emerged as a significant synthetic tool in organic synthesis.[10] As shown in Scheme 1, both isocyanide or phosphine can act as good nucleophiles to trigger the allenoate forming the reactive zwitterionic species, which is then trapped by electron-poor double bonds to produce stable five-membered rings. The main difference lies in the fact that isocyanide also participates in the ring formation as C1 building blocks, whereas the phosphine catalyst finally eliminates from the cycloadduct.

Notably, in 2003 Kwon and co-workers found that when alkyl-substituted allenoate was used, a novel phosphine-catalyzed [4+2] other than [3+2] annulation would take place to generate tetrahydropyridines (Scheme 1).[11] This strategy was further expanded to the syntheses of other six-membered rings and employed as a key step in the total synthesis of many natural products.[12] The key step in the [4+2] cycloaddition is believed to be the [1,3]-hydrogen shift process, which has been verified by computational analysis.[13] Accordingly, inspired by the great success of phosphine-catalyzed cycloadditions and our continuous interest in multicomponent reactions based on isocyanide and allenoate, we reasoned that introduction of a substituent at the α-position of allenoates might provide a new mechanism and exciting experimental results. As a continuation of our ongoing research,[8] herein we report that cascade multicomponent reactions of isocyanide, α-substituted allenoate, and methyleneindolinone can efficiently provide functionalized polycyclic compounds in a highly efficient manner under mild reaction conditions with broad substrate generality.

Spirocyclic oxindole is a significant synthetic motif that constitutes a large family of natural products and clinical pharma-

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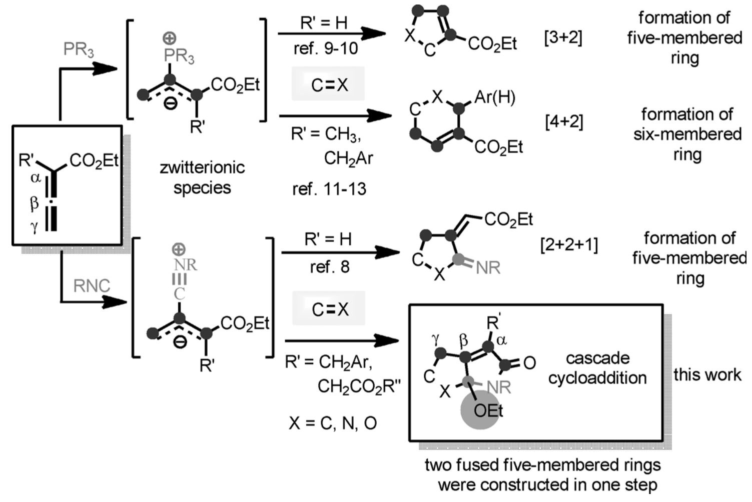
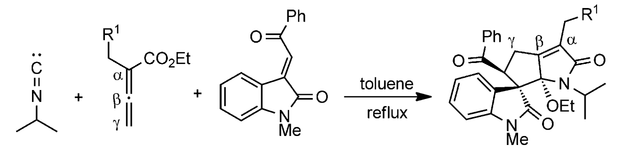


Scheme 1. Representative phosphine-catalyzed cycloadditions and isocyanide-based multicomponent reactions in the presence of allenoate and electron-deficient species.

ceuticals.[14] These compounds have demonstrated a broad range of biological activities, including insecticidal, antitumor, anthelmintic, and antibacterial properties.[15] In this regard, we selected the methyleneindolinones as the electron-poor alkenes to establish the basic methodology for the proposed three-component cycloaddition. As shown in Table 1, simply heating a solution of isopropyl isocyanide (**1a**), substituted ethyl 2,3-butadienoate **2a**, and methyleneindolinone **3a** in toluene under reflux directly provided the cycloadduct **4a** in 50% yield (Table 1, entry 1). The structure of compound **4a** was unambiguously confirmed by single-crystal X-ray analysis.[16] Subsequent solvent screening revealed that the solvent had a significant influence on the reaction yield: toluene was the most suitable solvent for the reaction, although xylene generally gave comparable results; solvents such as mesitylene, THF, and DMF only resulted in either a trace amount or none of the desired product. Reflux conditions were also required because the reaction yield decreased dramatically when the reaction was conducted under a lower temperature (e.g., 80 or 100 °C). Encouraged by this experimental result, we then explored the feasibility of allenoates bearing different substitution patterns. To our delight, broad generality was observed with various substituted allenoates **2** and several characteristics of this multicomponent cycloaddition reaction were noteworthy. As shown in Table 1, allenoates **2** with substituted benzyl (Table 1, entries 2–8) and $-CH_2CO_2R$ (entries 10–11) groups at the 2-position all worked well to yield the cycloadduct **4**.[17] On the contrary, no corresponding cycloadduct **4** was observed when allenoate with only a methyl group substituted (entry 9) was used. These results indicated that the presence of a conjugation stablizing group, such as an aryl or ester group, in the R^1 substituent was necessary for the whole conversion. In addition, varying the aryl group in the R^1 substituent also demonstrated that the present reaction proceeded best when allenoates **2** containing electron-withdrawing groups (e.g., hal, nitro; entries 2–6) were utilized, whereas the electron-rich groups gave lower yields (entries 7–8). It was also important to point out that the present protocol represented an unprecedented and valuable multicomponent example with excellent synthetic efficiency. Whereas allenoate was often used as a C2 and C3 component in previous transformations, the allenoate bearing an alkyl group acted as C4 building block to form two fused rings, which was very rare.[18]

Table 1. Three-component cascade cycloaddition of isocyanide **1a**, α-substituted allenoate **2**, and methyleneindolinone **3a**.[a]

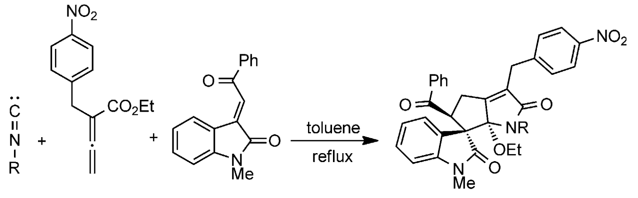


1a **2** **3a** **4**

Entry	R^1	Product	Yield [%][b]
1	C_6H_5	**4a**	50
2	$3\text{-}FC_6H_4$	**4b**	41
3	$3\text{-}ClC_6H_4$	**4c**	62
4	$4\text{-}BrC_6H_4$	**4d**	54
5	$3\text{-}NO_2C_6H_4$	**4e**	64
6	$4\text{-}NO_2C_6H_4$	**4f**	71
7	$2\text{-}MeC_6H_4$	**4g**	18
8	$4\text{-}MeC_6H_4$	**4h**	24
9	H	–	n.r.
10	CO_2Me	**4i**	46
11	CO_2Et	**4j**	51

[a] All reactions were carried out with isocyanide **1a** (0.5 mmol), allenoate **2** (0.6 mmol), and methyleneindolinone **3a** (0.5 mmol) in toluene (5 mL) and heated under reflux. [b] Yields of product after silica gel chromatography.

Table 2. Three-component cycloaddition reaction of isocyanide **1**, α-substituted allenoate **2f**, and methyleneindolinone **3a**.[a]



1 **2f** **3a** **5**

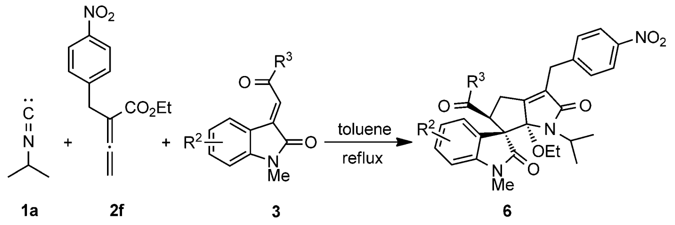
Entry	R	Product	Yield [%][b]
1	*tert*-butyl	**5a**	67
2	*n*-butyl	**5b**	81
3	Cyclohexyl	**5c**	50
4	1,1,3,3-tetramethylbutyl	**5d**	60
5	4-bromophenyl	**5e**	62
6	4-methoxyphenyl	**5f**	74
7[c]	2,6-dimethylphenyl	**5g**	27
8[c]	2-chloro-6-methylphenyl	**5h**	19

[a] Reaction conditions: isocyanide **1** (0.5 mmol), allenoate **2f** (0.6 mmol), methyleneindolinone **3a** (0.5 mmol), toluene (5 mL), reflux, 36 h. [b] Yields of product after silica gel chromatography. [c] The reaction time was prolonged to 48 h.

After having demonstrated a broad scope for substituted allenoates, a series of aliphatic and aromatic isocyanides **1** were next tested to react with allenoate **2 f** and methyleneindolinone **3 a**. The experimental results are summarized in Table 2. Notably, the structure of compound **5 a** was unambiguously confirmed by single-crystal X-ray analysis.[19] The reaction of *n*-butyl isocyanide **1 c**, for instance, furnished the cycloadduct **5 b** in 81 % yields (Table 2, entry 2). Gratifyingly, less reactive 4-bromophenyl isocyanide underwent a similar transformation to yield product **5 e** in good yield (entry 5). Sterically demanding aromatic isocyanides, such as 2,6-dimethylphenyl and 2-chloro-6-methylphenyl isocyanides, were also found to be compatible with this cascade cycloaddition protocol albeit with diminished yield and prolonged reaction time (entries 7–8).

To further explore the versatility of this multicomponent cycloaddition strategy, we turned our attention to the possibility of substituted methyleneindolinones **3**. As shown in Table 3, various methyleindolinones **3** with different substituents all proceeded readily underwent the cascade addition. Substrate **3** with an aliphatic unit ($R^3 = Me$) was also examined (Table 3, entry 6).

Table 3. Three-component reaction of isocyanide **1 a**, α-substituted allenoate **2 f**, and methyleneindolinone **3**.[a]

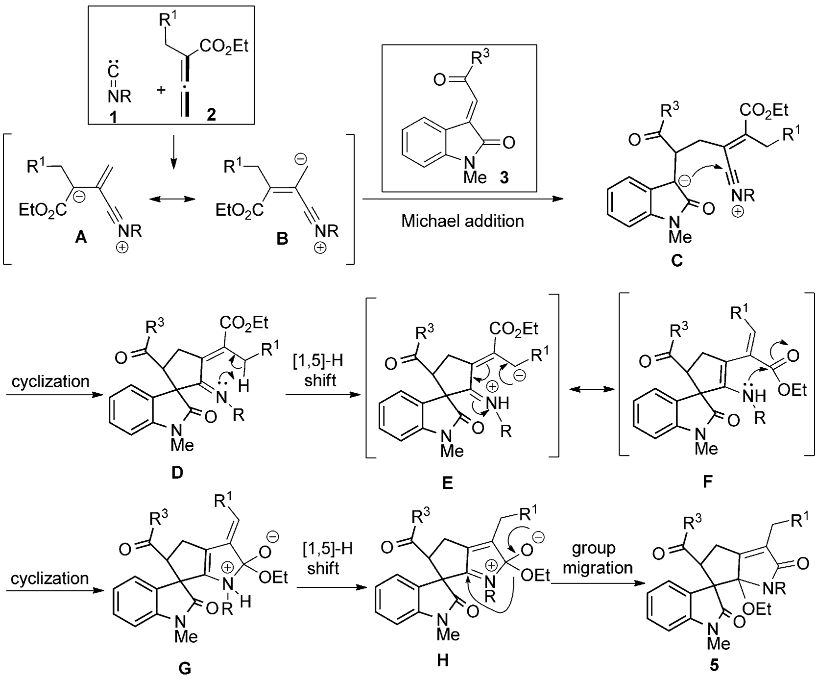


Entry	R^2	R^3	Product	Yield [%][b]
1	H	2-ClC_6H_4	**6 a**	71
2	H	4-ClC_6H_4	**6 b**	63
3	H	2-MeC_6H_4	**6 c**	44
4	H	3-$MeOC_6H_4$	**6 d**	84
5	H	4-$MeOC_6H_4$	**6 e**	67
6	H	CH_3	**6 f**	75
7	5-chloro	C_6H_5	**6 g**	66
8	5-bromo	C_6H_5	**6 h**	72
9	5-methoxy	C_6H_5	**6 i**	47
10	6-bromo	C_6H_5	**6 j**	68
11	4-bromo	C_6H_5	**6 k**	31

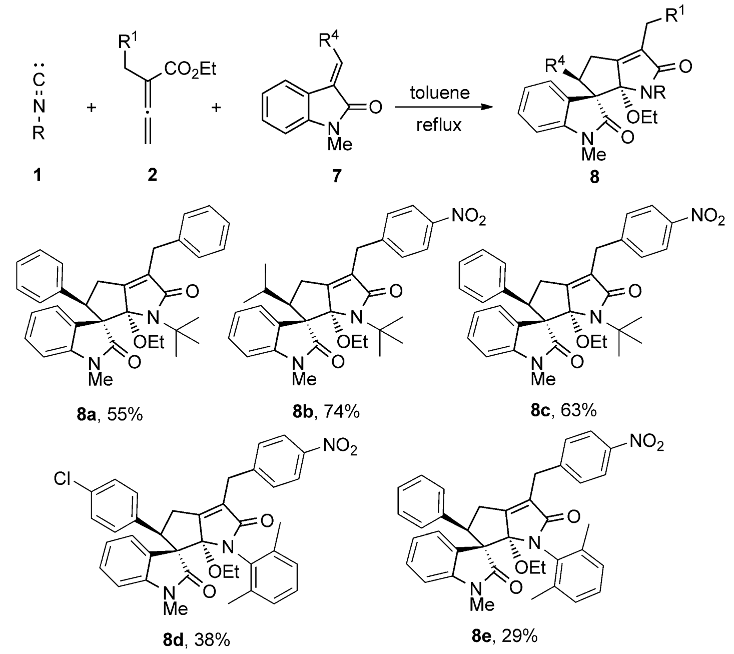
[a] Reaction conditions: isocyanide **1 a** (0.5 mmol), allenoate **2 f** (0.6 mmol), methyleneindolinone **3** (0.5 mmol), toluene (5 mL), reflux, 36 h. [b] Yields of product after silica gel chromatography.

The mechanism of this cycloaddition reaction has not been unequivocally established, but one reasonable possibility is proposed in Scheme 2. The beginning of the reaction involves the formation of reactive zwitterionic species, which exist as a resonance-stabilized form **A**↔**B**.[8a–c] The allylic carbanion **B** then adds to the carbon–carbon double bond of substrate **3** to produce intermediate **C**. Since the imine nitrogen atom in intermediate **D** can act as a base to abstract the acidic proton, it is reasonable to deduce that the [1,5]-hydrogen shift[20] then takes place to form **E** via a six-membered ring transition state.[13] This process also explains the fact that the present multicomponent reaction works well if the allenoate bears an R^1 group (aryl or carbonyl group) that can stabilize the anion formed in intermediate **E**. Subsequently, the more stable resonance form **F** undergoes the second-time intramolecular cyclization and [1,5]-hydrogen shift to yield intermediate **H**. Finally, the concerted ethoxy group migration essentially leads to the formation of product **5**.[21] From the proposed mechanism we can see that the installation of an alkyl group to allenoate is crucial to the present cascade reaction although the alkyl group does not directly provide the carbon component for the ring formation. In fact, this group participates in the cascade reaction in a quite special way by facilitating a sequenced [1,5]-hydrogen shift and subsequent annulation.[22] To some extent, the role of the alkyl substituent of allenoate **2** can also be considered as a directing group, which is quite different from the reported examples.

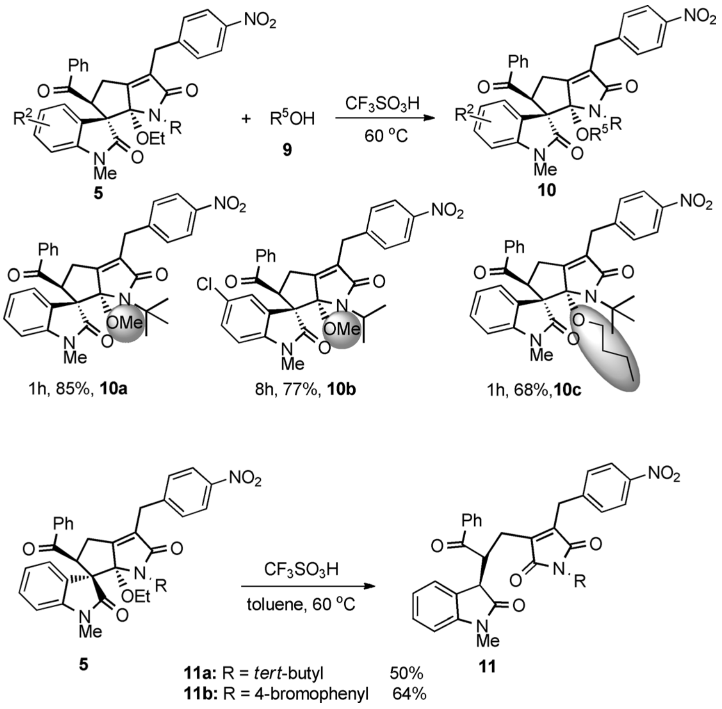
To further establish the scope and limitation of this method, electron-deficient alkenes **7** derived from oxindoles and alde-



Scheme 2. Proposed mechanism for the three-component reaction.



Scheme 3. Multicomponent reaction with expanded electron-deficient alkenes **7**.



Scheme 4. Further application of the cycloaddition product **5**.

hydes were also examined (Scheme 3). All of the tested new substrates **7** served as excellent substrates to react with isocyanide and substituted allenoate, producing the cycloadduct **8** in an efficient manner. Considering the readily variability of aldehyde, the increased new reactant dimension makes the present reaction more flexible, which is very significant for the fast and efficient construction of the corresponding compound library.

The formed cycloadducts **5** were also subjected to further conversion to demonstrate the potential applications of this method. As shown in Scheme 4, the ethoxy group can be easily replaced by other alkyl groups under acidic conditions in the presence of excessive alcohols. This reaction performed well with linear alcohols, but the alcohol with a side chain, such as *tert*-butyl alcohol, failed to yield the expected product **10**. A very interesting product, **11**, was also obtained under acidic conditions without the addition of alcohol. In this case, the structures of compound **11 a** was unambiguously confirmed by single-crystal X-ray analysis.[23] To our surprise, one of the five-membered rings opened together with the cleavage of one carbon–carbon single bond.

In conclusion, we have described a concise multicomponent reaction of isocyanide, α-substituted allenoate, and methyleneindolinone. The cascade sequence seems to comprise of a double Michael addition, double cyclization, and double [1,5]-hydrogen shift followed by group migration, thereby offering a fast and straightforward approach to unusual spirocyclic oxindoles. The present multicomponent strategy is also featured by the high synthetic efficiency since the substituted allenoate contributes four carbon atoms (C4) for the ring formation. Another remarkable characteristic of this methodology is that each of the three components can be readily varied, thus enabling the efficient preparation of a large number of compounds. For this reason, further works may include constructing a compound library and conducting an investigation on the structure–activity relationship (SAR). Extension of the present strategy to other electron-poor systems is still in progress in our lab.

Experimental Section

Typical procedure

Methyleneindolinone **3** (0.5 mmol) was added to a solution of isocyanide **1** (0.5 mmol) and allenoate **2** (0.6 mmol) in 5 mL toluene. The stirred mixture was heated under reflux for several hours and the progress was monitored by using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (silica: 200–300; eluant: petroleum ether/ethyl acetate) to afford the desired product.

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Keywords: allenoates · hydrogen shift · isocyanides · multicomponent reactions · spirocyclic oxindoles

[1] For recent examples, see: a) Y. Odabachian, S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 11078 – 11082; *Angew. Chem. Int. Ed.* **2013**, *52*, 10878 – 10882; b) T. Buyck, Q. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 12946 – 12950; *Angew. Chem. Int. Ed.* **2013**, *52*, 12714 – 12718; c) C.-H. Lei, D.-X. Wang, L. Zhao, J. Zhu, M.-X. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 4708 – 4711; d) A. Zajdlik, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer, A. K. Yudin, *Angew. Chem.* **2013**, *125*, 8569 – 8573; *Angew. Chem. Int. Ed.* **2013**, *52*, 8411 – 8415; e) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257 – 5269; f) T. Okitsu, K. Nagase, N. Nishio, A. Wada, *Org. Lett.* **2012**, *14*, 708 – 711; g) T. Vlaar, P. Mampuys, M. Helliwell, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *J. Org. Chem.* **2013**, *78*, 6735 – 6745.

[2] For palladium-catalyzed insertion of isocyanide, see: a) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem.* **2013**, *125*, 7222 – 7236; *Angew. Chem. Int. Ed.* **2013**, *52*, 7084 – 7097; b) M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835 – 4840; c) G. V. Baelen, S. Kuijer, L. Rýček, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2011**, *17*, 15039 – 15044; for other metal-catalyzed insertion, see: d) M. Zhang, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 4498 – 4499; e) W. D. Jones, W. P. Kosar, *J. Am. Chem. Soc.* **1986**, *108*, 5640 – 5641.

[3] For construction of heterocycles, see: indole: a) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270 – 4273; for a review on syntheses of indoles from isocyanides, see: b) J. Campo, M. Garcia-Valverde, S. Marcaccini, M. J. Rojo, T. Torroba, *Org. Biomol. Chem.* **2006**, *4*, 757 – 765; Oxazole: c) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 835 – 838; *Angew. Chem. Int. Ed.* **2003**, *42*, 811 – 814; d) O. V. Larionov, A. de Meijere, *Angew. Chem.* **2005**, *117*, 5809 – 5813; *Angew. Chem. Int. Ed.* **2005**, *44*, 5664 – 5667; e) A. V. Lygin, O. V. Larionov, V. S. Korotkov, A. de Meijere, *Chem. Eur. J.* **2009**, *15*, 227 – 236; Imidazole: f) C. J. Helal, J. C. Lucas, *Org. Lett.* **2002**, *4*, 4133 – 4134; g) C. Kanazawa, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10662 – 10663; h) A. M. van Leusen, J. Wildeman, O. H. Oldenyiel, *J. Org. Chem.* **1977**, *42*, 1153 – 1159.

[4] This unique property is also shared with carbon monoxide and formally divalent carbenes.

[5] a) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé, Eds.), Wiley-VCH, Weinheim, Germany, **2005**; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321 – 3329; c) R. V. A. Orru, M. De Greef, *Synthesis* **2003**, 1471 – 1499; d) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628 – 1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602 – 1634; e) A. Dömling, *Chem. Rev.* **2006**, *106*, 17 – 89; f) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444 – 8454; g) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300 – 1308; h) B. B. Toure, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439 – 4486; i) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358 – 6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234 – 6246.

[6] For atom economy: a) B. M. Trost, *Science* **1991**, *254*, 1471 – 1477; for step economy: b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40 – 49; for redox economy: c) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938 – 17954.

[7] a) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133 – 1144; to invent new multicomponent reactions from known MCR reactions is another significant strategy, see: b) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463 – 472.

[8] a) J. Li, Y. J. Liu, C. J. Li, X. S. Jia, *Chem. Eur. J.* **2011**, *17*, 7409 – 7413; b) J. Li, Y. J. Liu, C. J. Li, X. S. Jia, *Adv. Synth. Catal.* **2011**, *353*, 913 – 917; c) J. Li, N. Wang, C. J. Li, X. S. Jia, *Chem. Eur. J.* **2012**, *18*, 9645 – 9650; d) J. Li, N. Wang, C. J. Li, X. S. Jia, *Org. Lett.* **2012**, *14*, 4994 – 4997; e) J. Li, S. K. Su, M. Y. Huang, B. Y. Song, C. J. Li, X. S. Jia, *Chem. Commun.* **2013**, *49*, 10694 – 10696.

[9] C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906 – 2908.

[10] For reviews, see: a) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535 – 544; b) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102 – 3116. for applications in total synthesis, see: c) Y. Du, X. Lu, *J. Org. Chem.* **2003**, *68*, 6463 – 6465; d) J.-C. Wang, M. J. Krische, *Angew. Chem.* **2003**, *115*, 6035 – 6037; *Angew. Chem. Int. Ed.* **2003**, *42*, 5855 – 5857; e) T. Q. Pham, S. G. Pyne, B. W. Skelton, A. H. White, *J. Org. Chem.* **2005**, *70*, 6369 – 6377; for asymmetric variants, see: f) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454 – 1457; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426 – 1429; g) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660 – 5661; h) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988 – 10989; i) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem.* **2010**, *122*, 4569 – 4572; *Angew. Chem. Int. Ed.* **2010**, *49*, 4467 – 4470.

[11] X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716 – 4717.

[12] a) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234 – 12235; b) Y. S. Tran, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12632 – 12633; c) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 5843 – 5845; d) T. Wang, S. Ye, *Org. Lett.* **2010**, *12*, 4168 – 4171.

[13] a) Y. Qiao, K.-L. Han, *Org. Biomol. Chem.* **2012**, *10*, 7689 – 7706; b) L. Zhao, M. Wen, Z.-X. Wang, *Eur. J. Org. Chem.* **2012**, 3587 – 3597.

[14] For reviews, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209 – 2219; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127 – 139; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902 – 8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748 – 8758; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369 – 396; e) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381 – 1407.

[15] a) T. J. Greshock, A. W. Grubbs, P. Jiao, D. T. Wicklow, J. B. Gloer, R. M. Williams, *Angew. Chem.* **2008**, *120*, 3629 – 3633; *Angew. Chem. Int. Ed.* **2008**, *47*, 3573 – 3577; b) H. Venkatesan, M. C. Davis, Y. Altas, ##. Snyder, D. C. Liotta, *J. Org. Chem.* **2001**, *66*, 3653 – 3661; c) M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077 – 16086; d) S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165 – 193.

[16] CCDC-983301 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] See the Supporting Information for details.

[18] It should be pointed out that a substituted allenoate also serves as a C4 component in phosphine-catalyzed [4+2] cycloaddition by using one carbon atom in the alkyl substituent for the ring formation, which was different from the present multicomponent reaction.

[19] CCDC-983302 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] a) W. v. E. Doering, E. J. Keliher, X. Zhao, *J. Am. Chem. Soc.* **2004**, *126*, 14206 – 14216; b) M. Alajarín, B. Bonillo, P. Sánchez-Andrada, Á. Vidal, *J. Org. Chem.* **2010**, *75*, 3737 – 3750; c) M. Alajarín, B. Bonillo, M.-M. Ortín, P. Sánchez-Andrada, Á. Vidal, *Org. Lett.* **2006**, *8*, 5645 – 5648.

[21] In this process, a mechanism by step also cannot be ruled out.

[22] In the chemistry of isocyanide-based multicomponent reactions, the most popular [1,*n*]-hydrogen shift normally occurs to afford more stable aromatic rings, such as pyrrole and furan rings. This meant that the reaction generally terminated when the [1,*n*]-hydrogen shift finished.[5,7] In this case, however, the [1,5]-hydrogen shift process is quite different from the traditional ones since the [1,5]-hydrogen shift serves as the driving force for subsequent cascade transformation.

[23] CCDC-983303 (**11a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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COMMUNICATION

Organic Synthesis

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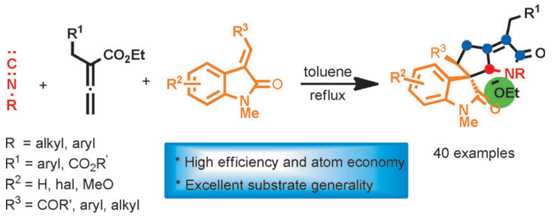
Isocyanide-Based Multicomponent Reactions: Concise Synthesis of Spirocyclic Oxindoles with Molecular Complexity by Using a [1,5]-Hydrogen Shift as the Key Step



Shift your perspective! An unprecedented cascade reaction, under mild conditions, involving a double Michael addition, double cyclization, and double [1,5]-hydrogen shift, followed by group migration is disclosed. This reaction offers a fast and straightforward approach to unusual polycyclic spirooxindoles (see scheme).