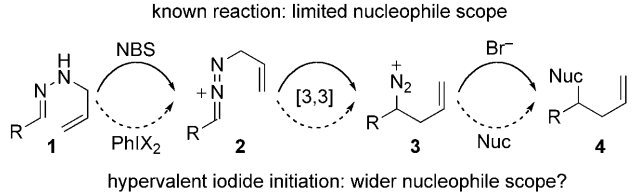
Synthetic Methods

DOI: 10.1002/ange.201100888

A Hypervalent Iodide-Initiated Fragment Coupling Cascade of *N*-Allylhydrazones**

*Kelly E. Lutz and Regan J. Thomson**

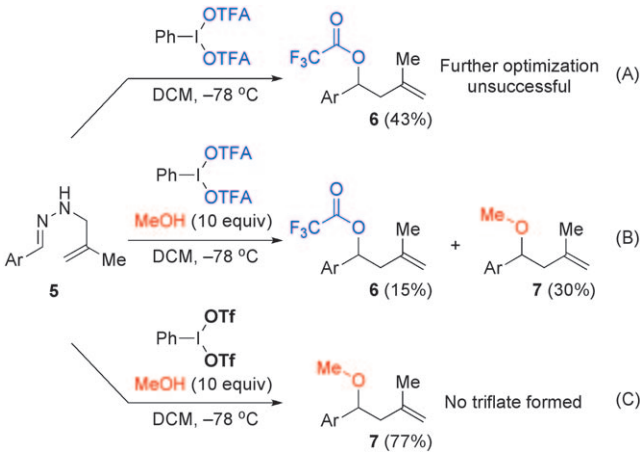
Reliable bond-forming reactions that enable the union of two or more molecular fragments are essential for the efficient and convergent assembly of complex natural products or medicinal agents.[1] As part of a program aimed at developing such reactions, we have been investigating the utility of *N*-allylhydrazides as versatile chemical intermediates that allow for high yielding fragment coupling by way of hydrazone formation followed by a carbon–carbon bond-forming molecular rearrangement.[2] Most recently, we reported a triflimide-catalyzed rearrangement of *N*-allylhydrazones (the Stevens [3,3] rearrangement)[3] that allows for a "traceless" bond construction between two fragments.[2c] Prior to this development, we reported an *N*-bromosuccinimide (NBS)-initiated rearrangement that not only allowed for such fragment assembly but also incorporated an additional bromide atom (i.e., **1**→**4**, Nuc = Br).[2b] We speculated that *N*-bromination, followed by loss of bromide, initiated the cascade sequence through diazoallene species **2** (Scheme 1). A [3,3] sigmatropic rearrangement would afford diazonium ion **3**, which would react with bromide to produce the benzylic bromide **4** (Nuc = Br).



Scheme 1. Cascade sequences of N-allylhydrazones.

We wished to widen the scope of this cascade sequence to include other nucleophiles, and were especially intrigued by the possibility of initiating the hydrazone oxidation (i.e., **1**→**2** in Scheme 1) with hypervalent iodine compounds (i.e., $PhIX_2$ where X = OAc, OTFA, OTf, etc).[4] We anticipated that the nucleophile in such a system might not necessarily be limited to the coordinated ligand on the iodine atom, providing a useful and powerful strategy to couple multiple species together (i.e., an aldehyde, an allylhydrazide, and the nucleophile).

We initiated our research efforts in this new area by investigating the effects of the commercially available hypervalent iodine compounds, $PhI(OAc)_2$ (PIDA) and $PhI(OTFA)_2$ (PIFA; OTFA = trifluoroacetate), on the hydrazone derived from the condensation of 2-naphthaldehyde and methylallyl hydrazine (i.e., **5**; Scheme 2). While PIDA gave



Scheme 2.

no desired product under the conditions explored, PIFA provided trifluoroacetate **6** (X = OTFA) in 43% yield (Scheme 2A). This low-yielding result, which could not be improved upon, provided initial evidence that hypervalent iodides were able to promote rearrangements of *N*-allylhydrazones. It was during an investigation of various exogenous nucleophiles that we ran the reaction between hydrazone **5** and PIFA, in the presence of methanol (10 equiv), and observed formation of the ester **6**, along with competitive formation of ether **7** (Scheme 2B). While it was possible to favor generation of the ether adduct by using methanol as the solvent, this would limit the use of this method to readily available alcohols, and would preclude the use of solid alcohols or those that are part of a more complex fragment. Therefore, we explored the use of $PhI(OTf)_2$ as an initiator,[5] reasoning that the much less nucleophilic triflate would not compete with the alcohol for incorporation into the substrate.[6] In the event, we found that exposure of hydrazone **5** to one equivalent of $PhI(OTf)_2$ (formed in situ by the addition of TMSOTf to iodosobenzene)[5] in the presence of methanol

[*] K. E. Lutz, Prof. R. J. Thomson
Department of Chemistry, Northwestern University
2145 Sheridan Rd, Evanston, IL 60208 (USA)
Fax: (+1) 847-467-2184
E-mail: r-thomson@northwestern.edu

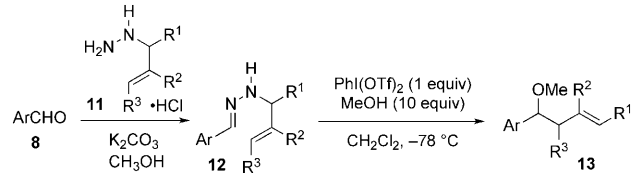
[**] This work was supported by Northwestern University (NU), Amgen, and the National Science Foundation (NSF, CHE0845063). We thank Colleen McGourty (NU) and Devon Mundal (NU) for early contributions.

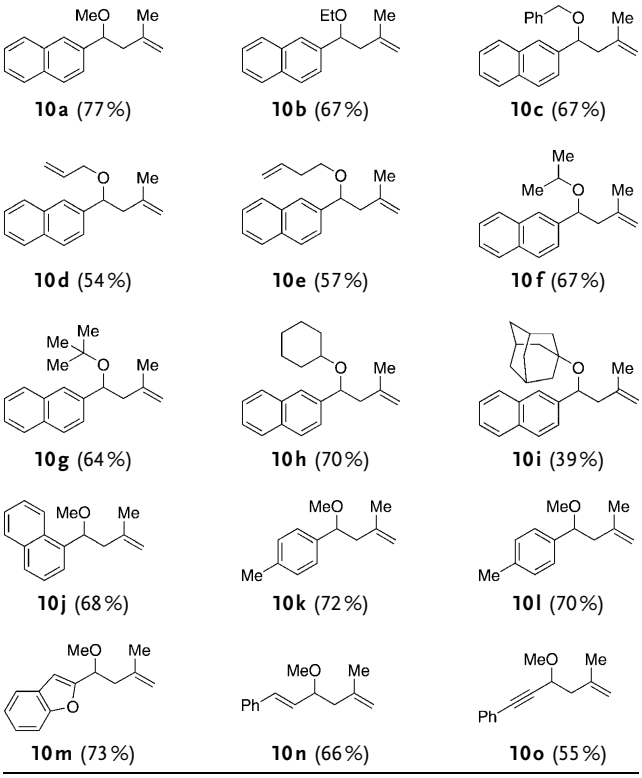
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100888.

(10 equiv) led to smooth formation of the desired ether **7** in 77% yield with no discernable trace of the corresponding triflate (Scheme 2C).

Under the developed conditions, a number of ethers could be formed using various alcohols and aldehydes (Table 1). Using 2-naphthaldehyde as the basic test substrate, the process proved effective for incorporation of a number of primary alcohols, including those possessing handles for future manipulation. For example, one could envision that substrates **10d** and **10e** (Table 1) could readily undergo ring-closing metathesis to form cyclic ethers.[7] Branched alcohols are well tolerated (**10f–10i**), including cyclic alcohols. Remarkably, both *tert*-butanol and 1-adamantol afforded the corresponding ethers (Table 1, **10g** and **10i**), although 1-adamantol gave a diminished yield over the two-step procedure from 2-naphthaldehyde (Table 1, **10i**). Attempted incorporation of phenols was unsuccessful, presumably due to rapid oxidation and decomposition of the alcohol. Likewise, the use of other oxidation prone nucleophiles such as amines, led to no desired products.

Table 1: Aldehyde and alcohol variation in the $PhI(OTf)_2$-initiated cascade.[a]



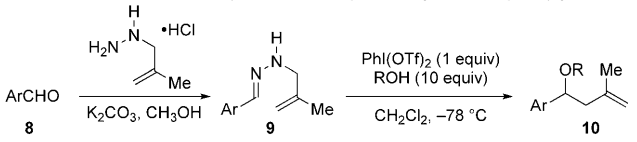


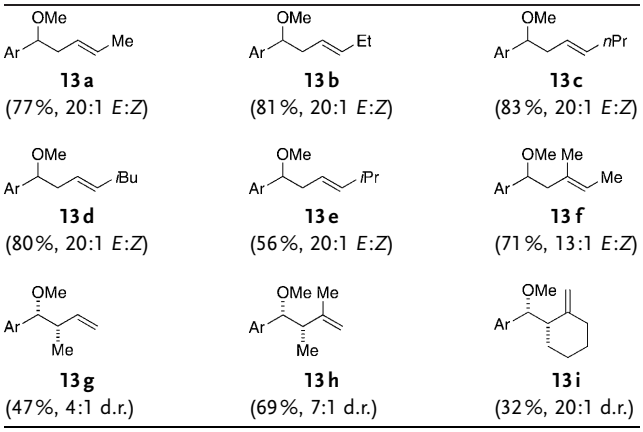
[a] Yields of isolated product over two steps from aldehyde **8**. The intermediate hydrazone **9** was not purified prior to hypervalent iodide-initiated rearrangement. OTf = trifluoromethanesulfonate.

The process proved reliable for several additional aryl aldehydes (i.e., Table 1, **10j–10m**) and could also be conducted on α,β-unsaturated aldehydes in good yield (i.e., Table 1, **10n** and **10o**). The use of electron-deficient aryl hydrazones such as that derived from 4-bromobenzaldehyde was possible, but produced low yields of the desired adducts. Similarly, attempts to utilize saturated aldehydes met with little success due to the particular instability of the intermediate hydrazones.

We next investigated the use of different hydrazine substrates, in order to establish protocols for stereoselective alkene synthesis, and diastereoselective formation of vicinal stereocenters (Table 2). As anticipated, hydrazones that possessed a substituent attached to the same carbon as the nitrogen atom (i.e., Table 2, **13a–13e**), provided the desired ethers with >20:1 selectivity for the *E*-isomer.[8] A trisubstituted alkene was formed with high levels of stereoselectivity and in good yield (Table 2, **13f**). In addition to stereoselective alkene formation, we showed that vicinal stereoarrays could be produced with modest to good levels of stereoselectivity when the hydrazide fragment possessed a methyl group at the alkene terminus (Table 2, **13g–13i**). While the efficiency of these last two-step couplings were somewhat modest, substrate **13g** was formed with the *syn*-isomer as the major diastereomer,[9] which provided some useful insight into the possible mechanism of this transformation (see Scheme 3).

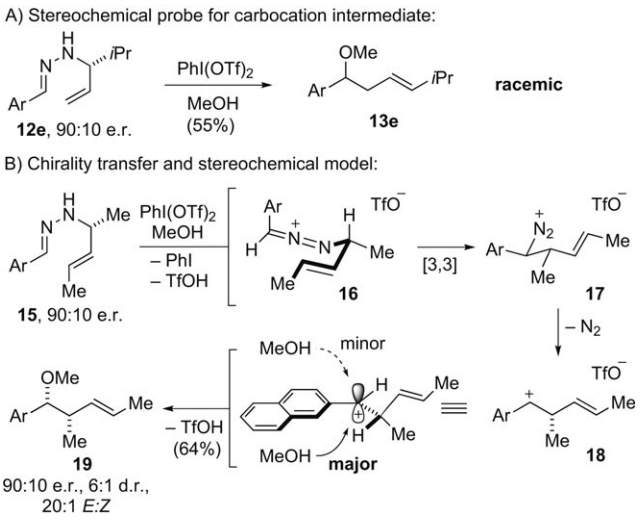
Table 2: Variation of the hydrazide component (Ar = 2-naphthyl).[a]



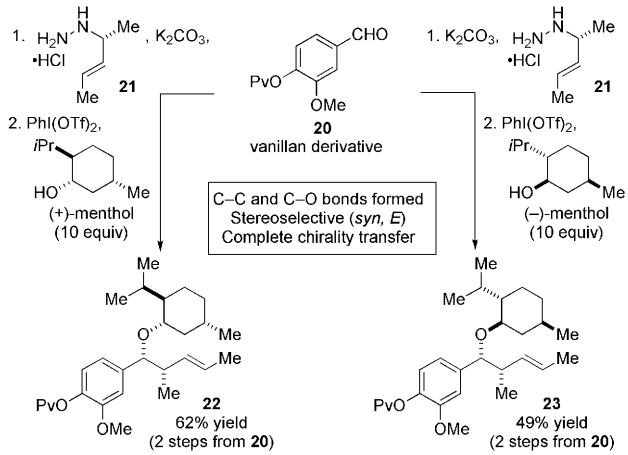


[a] Yields of isolated product over two steps from ArCHO (**8**). *E*:*Z* ratios determined by ^{1}H NMR spectroscopy; d.r. refers to ratio of the *syn* isomer to *anti* isomer.

The mechanistic hypothesis outlined in Scheme 1 involves the intermediacy of a benzylic diazonium ion, which under the reaction conditions is likely to ionize and thus produce a reactive carbocation. As a stereochemical probe for the intermediacy of a carbocation, we prepared chiral nonracemic hydrazone **12e** (90:10 e.r., Ar = 2-naphthyl)[10] and exposed it



Scheme 3. Stereochemical probes for the reaction (Ar = 2-naphthyl).



Scheme 4. Fragment coupling of natural products. Pv = pivoyl.

to the reaction conditions (Scheme 3 A). The product **13e** was produced as a racemate, providing evidence of an achiral carbocation intermediate. While this experiment showed that stereoinduction from the hydrazide fragment could not be relayed directly to the newly formed oxygen stereocenter, we prepared chiral non-racemic hydrazone **15** (90:10 e.r., Ar = 2-naphthyl)[11] in order to test the prospect of stereochemical transfer to the newly formed carbon sterocenter, and hence to the oxygen center following diastereoselective alcohol incorporation (Scheme 3 B). In the event, hydrazine **15** generated the desired product (i.e., **19**) as a single alkene isomer, in a 6:1 ratio of *syn*:*anti* diastereomers, but more importantly with complete transfer of chirality (90:10 e.r.).[12]

This remarkable transformation forms a C–C bond and a C–O bond, generates a stereodefined alkene, and produces two new vicinal stereocenters with a high level of diastereocontrol and enantioselectivity. The absolute sense of stereoinduction in the formation of ether **19** is consistent with transfer of chirality through a chair-like transition state,[13] possibly resembling **16**. Formation of the *trans* alkene is also consistent with such a chair-like transition state. Since our experimental results provide evidence for C–O bond formation by an S_N1 mechanism (see Scheme 3), it is likely that the observed *syn* configuration is a result of the alcohol adding opposite the alkene substituent within the A(1,3) minimized carbocation **18**.[14] This notion is supported by the observed trend for enhanced diastereoselectivity as the alkene substituent inceases in size (see Table 2, compounds **14g, 14h**, and **14i**).

Finally, we wished to demonstrate that the reaction sequence may be used to couple more complex fragments, and in particular we were drawn to the notion of using this chemistry for the union of two natural products (Scheme 4). To this end, vanillan derivative **20** could be readily condensed with enantioenriched hydrazine **21** to form the corresponding hydrazone (not shown). Exposure of this hydrazone to $PhI(OTf)_2$ in the presence of (+)-menthol gave rise to the complex "natural product-like"[15] molecule **22** in 62 % yield from aldehyde **20**. Similarly, the diastereomeric compound **23** could be readily generated using the (−)-antipode of menthol in the sequence, thereby demonstrating the stereochemical diversity possible in just two steps using this new transformation. Curiously, the latter reaction using (−)-menthol proved less efficient than when (+)-menthol was used, perhaps indicating a matched and mismatched situation between the stereochemistry of each reacting partner.[16]

In conclusion, we have developed a unique hypervalent-iodide-initiated cascade process that enables the rapid union of an aldehyde, an allylic hydrazide, and an alcohol. A high degree of selectivity is observed for the formation of disubstituted alkenes, vicinal stereocenters, and in processes involving chirality transfer within non-racemic substrates. Complex "natural product-like" compounds may be synthesized in only a few steps using this chemistry suggesting that future applications to natural product synthesis or to diverse libraries for drug discovery may be a possibility.[15]

Received: February 3, 2011
Published online: April 6, 2011

Keywords: cascade reactions · hydrazones · hypervalent iodide reagents · stereoselective synthesis

[1] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.
[2] a) D. A. Mundal, J. J. Lee, R. J. Thomson, *J. Am. Chem. Soc.* **2008**, *130*, 1148–1149; b) D. A. Mundal, K. E. Lutz, R. J. Thomson, *Org. Lett.* **2009**, *11*, 465–468; c) D. A. Mundal, C. A. Avetta, Jr., R. J. Thomson, *Nat. Chem.* **2010**, *2*, 294–297.
[3] The thermal rearrangement of *N*-allylhydrazones was first reported by Stevens and co-workers in 1973, see: R. V. Stevens, E. E. McEntire, W. E. Barnett, E. Wenkert, *J. Chem. Soc. Chem. Commun.* **1973**, 662–663.
[4] For reviews regarding the chemistry of hypervalent iodide reagents, see: a) R. M. Moriarty, R. K. Vaid, *Synthesis* **1991**, 431–447; b) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, **1992**; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584; e) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123–1178.

[5] a) N. S. Zefirov, S. O. Safronov, A. A. Kaznacheev, V. V. Zhdankin, *Zh. Org. Khim.* **1989**, *25*, 1807 – 1808.
[6] The effect of counter-ions in some hypervalent iodide-mediated transformations has been reported, see: V. V. Zhdankin, R. Tykwinski, B. Berglund, M. Mullikin, R. Caple, N. S. Zefirov, A. S. Koz'min, *J. Org. Chem.* **1989**, *54*, 2609 – 2612.
[7] G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426 – 5427.
[8] Double bond geometry was determined by analysis of ^{1}H NMR coupling constants. See Supporting Information.
[9] The *syn* configuration was determined through direct comparison to an authentic sample prepared using the well established *syn*-selective crotylation of aldehydes developed by Roush and co-workers, see: W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339 – 6348. See Supporting Information for full details. Substrates **13h** and **13i** were assigned by analogy.
[10] The requisite hydrazine required for the formation of enantioenriched hydrazone **12e** was prepared through an enantioselective α-amination of 3-methylbutanal according to the procedure of List for related aldehydes, see; B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656 – 5657. See Supporting Information for full details.
[11] Prepared by using a variant of the Pd-catalyzed allylation reported by Trost and Du Bois, see: B. M. Trost, S. Malhotra, D. E. Olson, A. Maruniak, J. Du Bois, *J. Am. Chem. Soc.* **2009**, *131*, 4190 – 4191. See Supporting Information for full details.
[12] The relative and absolute configuration of **19** was determined through a chemical correlation. See Supporting Information for full details.
[13] Asymmetric induction in sigmatropic rearrangements was first reported for the Cope rearrangement by Hill and Gilman, see: R. K. Hill, N. W. Gilman, *J. Chem. Soc. Chem. Commun.* **1967**, 619 – 620.
[14] For a review of allylic strain as a controlling element in chemical transformations, see: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841 – 1860.
[15] The term "natural product-like" is used in fields such as chemical biology to describe scaffolds that have structural features related to natural products, see: A. M. Boldi, *Curr. Opin. Chem. Biol.* **2004**, *8*, 281 – 286.
[16] Attempts to use enantiopure chiral alcohols to directly induce stereoselectivity during the C–O bond-forming step using achiral hydrazone precursors only ever led to 1:1 mixtures of diastereomers.

