

Enantioselective Synthesis of *trans*-2,3-Dihydro-1*H*-indoles through C–H Insertion of α -Diazocarbonyl Compounds

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Abstract: A stereoselective synthesis of 2,3-dihydro-1*H*-indoles with a Rh(II) catalyzed C–H insertion is reported. The α -diazo carbonyl intermediates are obtained *via* a diazo-transfer reaction on 2-aminophenylacetic acids. Optimizations and kinetic studies were performed leading to increased yields of the diazo-transfer after mechanistic evaluation of the side product formation. *trans*-2,3-Dihydro-1*H*-indoles were obtained in high diastereomeric excesses (up to 94% *de*) and enantioselectivities (up to 94% *ee*).

Dihydroindoles (indolines) are constituents of many natural products and biologically active compounds, such as vinblastine,^[1] physostigmine^[2] and pentopril^[3] (Figure 1).

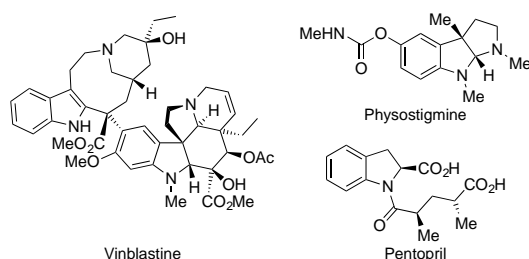


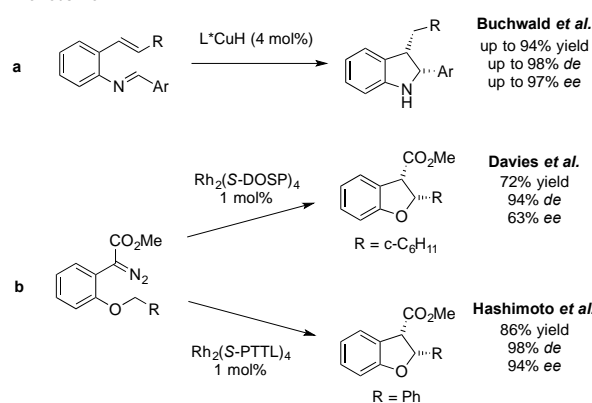
Figure 1. Examples of natural products and synthetic drugs containing the dihydroindole framework.

In the standard repertoire for the preparation of indolines are metal-catalyzed aryl aminations,^[4] intramolecular radical-mediated aryl aminations,^[5] as well as intramolecular carbolithiations.^[6]

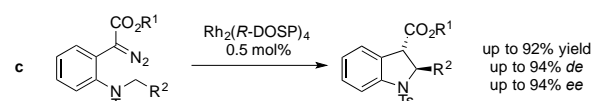
A very efficient and highly stereoselective Cu-catalyzed synthesis of *cis*-2,3-disubstituted indolines was recently reported by Asci and Buchwald (Scheme 1a).^[7] Davies *et al.*^[8] as well as Hashimoto and co-workers^[9] optimized the rhodium-catalyzed C–H insertion for the formation of chiral dihydrobenzofurans using

Rh₂(S-DOSP)₄ and Rh₂(S-PTTL)₄ as catalysts (Scheme 1b). In both cases, the *cis*-products were produced in high yields and with excellent diastereomeric and enantiomeric excesses.^[10] We report herein an efficient stereoselective synthesis for *trans*-2,3-dihydro-1*H*-indoles from α -diazo carbonyl compounds using Rh(II)-catalyzed intramolecular C–H insertions (Scheme 1c).

Previous work:



This work:



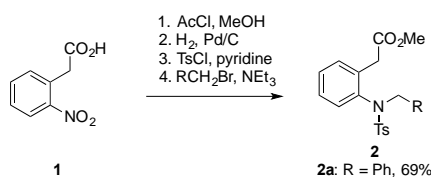
Scheme 1. Examples of asymmetric synthesis of heterocycles: a: Buchwald's asymmetric synthesis to *cis*-dihydroindoles; b: Rh(II)-catalyzed C–H insertion from α -diazo carbonyl compounds to dihydrobenzofuran; c: This work on the asymmetric synthesis of *trans*-dihydroindoles *via* C–H insertion.

Diazo, and particularly α -diazo carbonyl compounds, are well established as versatile intermediates in many chemical transformations,^[11] including C–C bond formation from the catalytic activation of C(sp³)-H bonds.^[12] The metal-catalyzed C–H insertion from aryl diazo acetates has been widely investigated in the last decade where chiral dirhodium(II) complexes have been shown to be the most efficient catalysts for the synthesis of optically active heterocycles.^[13] However, only a few reports describe indoline formation *via* carbene C–H insertions.^[14] We describe here the efficient synthesis of *trans*-dihydroindoles starting from the commercially available 2-nitrophenylacetic acid **1** (Scheme 3). The nitro group was chemoselectively reduced with hydrogen and Pd/C as with other reduction protocols side products were observed. The *N*-tosyl group was found to more stable than *N*-acetyl and *N*-boc derivatives (see supporting information). Subsequently, the optimization of the diazo transfer

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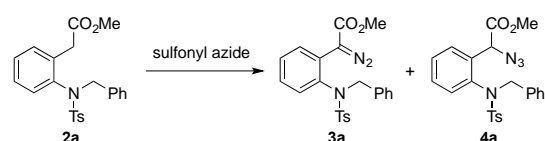
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reaction using **2a** as model substrate to obtain the diazo intermediate **3a** was investigated in detail (Table 1).



Scheme 2. Synthesis of starting materials **2**.

Table 1. Optimization of the diazo transfer conditions.^[a]



Entry	Sulfonyl azide (equiv.)	Base (equiv.)	Reaction conditions	3a [%] ^[b]	4a [%] ^[b]
1	<i>p</i> -ABSA (1.2)	DBU (1.7)	MeCN 22 °C, 24 h	36	45
2	mesyl azide (1.2)	DBU (1.7)	MeCN 22 °C, 24 h	0	0
3	<i>p</i> -NBSA (2)	DBU (2.5)	MeCN 22 °C, 48 h	50	18
4 ^[c]	<i>p</i> -NBSA (2)	DBU (2.5)	MeCN 22 °C, 48 h	63	13
5 ^[d]	<i>p</i> -NBSA (2)	DBU (2.5)	MeCN 22 °C, 48 h	53	29
6 ^[c]	<i>p</i> -NBSA (2)	DBU (2.5)	MeCN 45 °C, 48 h	65	0
7 ^[c]	<i>p</i> -NBSA (2)	DBU (2.5)	MeCN 65 °C, 24 h	63	0

[a] DBU was added to a solution of **2a** and sulfonyl azide. The reaction was quenched with sat. aq. NH₄Cl. [b] Isolated yield after column chromatography. [c] The reaction was quenched with a pH 7 phosphate buffer solution. [d] The reaction was quenched with a sat. aq. NaHCO₃.

Initially, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) was used as transfer reagent and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in acetonitrile since this combination has previously been reported in the efficient synthesis of aryl diazo acetates.^[15] We also have used the same combination for the generation of diazo compounds in flow systems.^[16] However, these conditions led to low yields and to the formation of azide **4a** as unexpected side product (Table 1, entry 1). The employment of different solvents, stronger bases such as LiHMDS or more reactive diazo transfer reagents such as mesyl azide (Table 1, entry 2) did not lead to any reaction (see supporting information). However, when *p*-nitrobenzenesulfonyl azide (*p*-NBSA) was used the product yield increased to 63%, especially when the reaction was quenched with a pH 7 phosphate buffer rather than with ammonium chloride (Table 1, entry 4). Higher temperatures appeared to avoid the side reaction yielding **3a** in comparable

yields (Table 1, entries 6-7), but at 65 °C there is some decomposition of **3a** and of *p*-NBSA in the presence of DBU.

The solid-state structures of the product **3a** and the side product **4a** were also determined by X-ray diffraction analysis (Figure 2).^[17] The complex ¹H NMR spectrum of **4a** suggests a 1:1 mixture of two rotamers due to the sterically encumbered amine nitrogen (see supporting information).

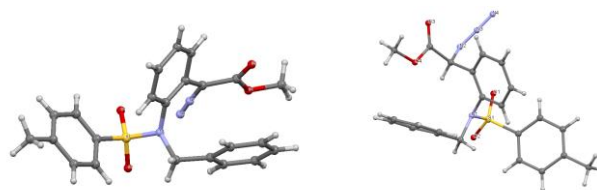
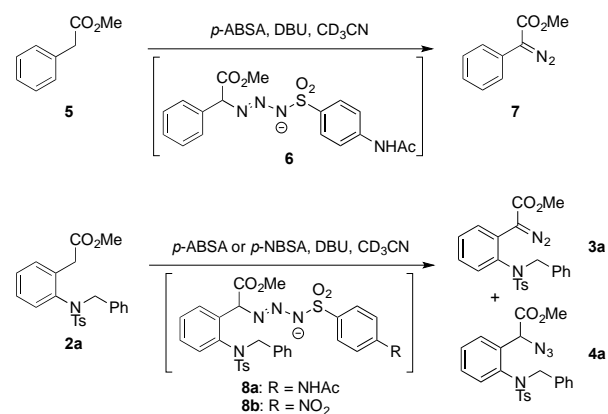


Figure 2. Solid state X-ray crystal structures of diazo compound **3a** (left) and of the azide **4a** (right).

To explain better the different behaviour of **2a** compared to other aryl acetate derivatives under similar diazo transfer conditions, the reaction progress for **2a** and methyl phenylacetate **5** was monitored by NMR spectroscopy (Scheme 3). These experiments show that **2a** and **5** are converted into intermediates **6** and **8**, whose decomposition lead to the diazo compounds **7** and **3a**, according to the mechanism reported in literature.^[18] Compared to **2a**, methyl phenylacetate **5** takes longer to form the triazene intermediate **6** with full conversion into **7** after 24 h. As soon as **6** is formed, a rapid cleavage to the diazo compound **7** occurs. We have not isolated intermediates **6** and **8**, but similar compounds have been shown to be useful precursors for the generation of diazo compounds under mild conditions.^[19]



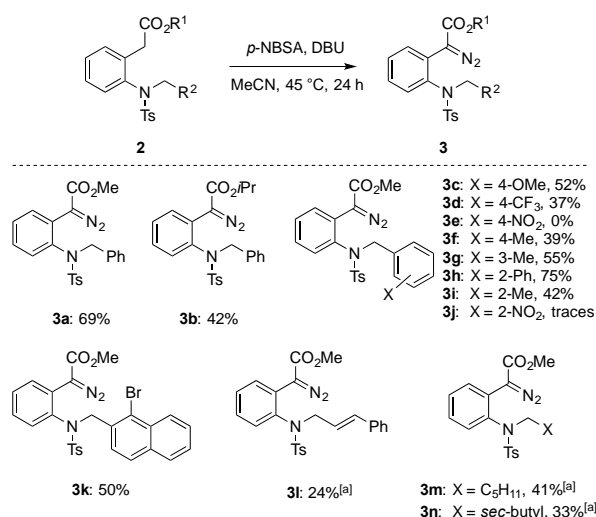
Scheme 3. The kinetic experiments were performed using a 300 MHz NMR spectrometer in CD₃CN (0.5 mL).

On the contrary, **2a** is completely converted into **8** within 60 min (**8a**) or 10 min (**8b**). Due to the higher stability of the intermediates **8**, their cleavage into the diazo product **3a** is slow.

The diazo derivative **3a** becomes detectable only after 22 h and is formed slowly (over 168 h), while a small amount of the azide **4a** can be detected after just 1 h.

The competition between the formation of **3a** and **4a** is attributed to the decomposition of the triazene during the work-up as previously described by Evans,^[20] as the triazene intermediate can be cleaved in two different pathways depending on the quenching agent.

In the synthesis of the starting materials **2** as shown in Scheme 2, it was possible to carry forward crude reaction mixtures with only final column purifications. Products **2** were obtained in moderate to good overall yields (37–82%). Most *N*-benzyl derivatives (**2a–k**) showed very good yields (>50%) compared to *N*-alkyl substrates (**2l–n**), which have been prepared using a Mitsunobu reaction in the alkylation step. With the optimized reaction conditions, the substrate scope of the diazo transfer reaction was examined and a series of compounds **3** was synthesized as shown in Scheme 4. Electron-donating and -withdrawing groups are tolerated except for the nitro-substituted derivatives (**2e** and **2j**) which gave complex product mixtures.



Scheme 4. Scope of the diazo-transfer reaction. [a] Yield determined by ¹H NMR.

Reasonable yields of the diazo compounds **3** have been obtained and the best conditions for the subsequent enantioselective C–H insertions to obtain the dihydroindole target compounds were then evaluated. Initial screening of catalysts and reaction conditions was performed with substrate **3a** using Rh₂(DOSP)₄, Rh₂(PTAD)₄ and Rh₂(PTTL)₄ as well-known catalysts for this type of C–H insertions.

Among all the screened conditions, the highest *ee* was achieved using Rh₂(DOSP)₄ as chiral catalyst at room temperature in *n*-hexane giving 11:1 *dr*, 86% *ee* (Table 2, entry 8). Surprisingly, performing the reaction at lower temperature showed a decrease in enantioselectivity, despite a significant improvement on the diastereomeric ratio (Table 2, entry 9).

The optimized reaction conditions were then used to synthesize **9a–k**. The dihydroindoles **9** were typically obtained in good yields and in good to excellent enantiomeric excesses. (Table 3).

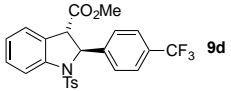
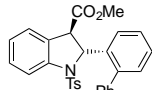
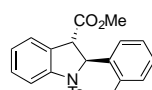
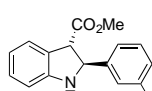
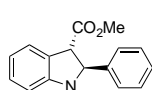
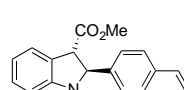
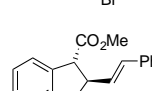
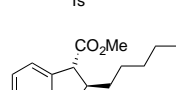
Table 2. Stereoselective C–H insertion of **3a** using rhodium(II) catalysts.^[a]

Entry	Rh(II) catalyst	Conditions	Yield [%] ^[b]	9a:10a ^[c]	<i>ee</i> 9a ^[d] [%]	<i>ee</i> 10a ^[d] [%]
1	Rh ₂ (OAc) ₄ 1 mol%	CH ₂ Cl ₂ 22 °C, 12 h	92	4:1	-	-
2	Rh ₂ (S-DOSP) ₄ 1 mol%	CH ₂ Cl ₂ 22 °C, 12 h	77	3.5:1	41	60
3	Rh ₂ (R-DOSP) ₄ 1 mol%	<i>n</i> -C ₆ H ₁₄ 22 °C, 12 h	81	13:1	83	0
4	Rh ₂ (R-DOSP) ₄ 1 mol%	<i>n</i> -C ₆ H ₁₄ 0 °C, 12 h	48	9:1	75	0
5 ^[e]	Rh ₂ (S-DOSP) ₄ 1 mol%	cyclohexane 22 °C, 12 h	full conv.	9.3:1	72	7
6	Rh ₂ (R-PTAD) ₄ 1 mol%	<i>n</i> -C ₆ H ₁₄ 22 °C, 12 h	18	1:1.1	58	40
7	Rh ₂ (S-PTTL) ₄ 1 mol%	<i>n</i> -C ₆ H ₁₄ 22 °C, 12 h	63	1:4	11	4
8	Rh ₂ (R-DOSP) ₄ 0.5 mol%	<i>n</i> -C ₆ H ₁₄ 22 °C, 24 h	82	11:1	86	0
9	Rh ₂ (R-DOSP) ₄ 0.5 mol%	<i>n</i> -C ₆ H ₁₄ 0 °C, 24 h	82	48:1	73	n.d.

[a] The reactions were performed on 0.12 mmol scale. [b] **9a** + **10a** isolated yield. [c] Determined by ¹H NMR. [d] Determined by HPLC. [e] Performed on 0.02 mmol scale, yield determined by ¹H NMR.

Table 3. Substrate scope of 1,2-dihydro-1*H*-indoles.^[a]

Entry	9	Yield (%) ^[b]	9:10 ^[c]	<i>ee</i> % ^[d]
1		82	11:1	86
2		62	2.2:1	35
3		80 ^[e]	35:1	66

4		9d	82	5:1	80
5		9e	37	13:1	94
6		9f	86	8:1	64
7		9g	73	8:1	71
8		9h	92	14:1	42
9		9i	48	6:1	75
10		9j	53	7:1	33
11		9k	64	>99:1	48

[a] Reactions performed according to the conditions shown in Table 2, entry 8. [b] Combined yield of **9** + **10**. [c] Determined by ¹H NMR. [d] Determined by HPLC. [e] 1 mol% catalyst used.

A bulkier ester seemed to have a negative impact on the asymmetric cyclization with a drop of both *de* and *ee* (**9b**). Both electron-donating and electron-withdrawing groups showed good conversion and stereoselectivity affording **9c-h** in good *ee* under the optimized reaction conditions. On the other hand, 2-

substituted aryl derivatives **9e** and **9i** were obtained with 72% *de* and >75% *ee*, but a slower conversion was observed.

In conclusion, we have developed a new synthetic pathway to afford *trans*-2,3-dihydro-1*H*-indoles from α -diazocarbonyl precursors in good yields and with high enantioselective excesses using a stereoselective Rh(II)-catalyzed C–H insertion.

Experimental Section

A solution containing the ester **2** (1 mmol) and *p*-NBSA (456 mg, 2 mmol) in CH₃CN (4 mL) was cooled to 0 °C. DBU (374 μ L, 2.5 mmol) was added dropwise. The reaction was stirred for 48 h at room temperature (or 45 °C). After completion (TLC), the reaction mixture was cooled to 0 °C and a pH 7 phosphate buffer (10 mL) was added. The mixture was extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic fractions were washed with pH 7 phosphate buffer (10 mL) and brine (15 mL) and dried over MgSO₄. The solvent was evaporated *in vacuo* at 30 °C and the crude reaction mixture purified *via* flash column chromatography to afford product **3**.

Molecular sieves (3 Å, 1.2 g), Rh₂(*R*-DOSP)₄ (4.4 mg, 0.002 mmol, 1 mol%) were dissolved in dry *n*-hexane (10 mL). Diazo compound **3** (0.23 mmol) was added and the reaction mixture was stirred at 22 °C under argon until all diazo compound was consumed (TLC). The reaction mixture was passed through a short silica plug which was washed with CH₂Cl₂ (3 x 5 mL). The reaction mixture was concentrated *in vacuo* and purified *via* column chromatography to afford dihydroindole **9**.

Acknowledgements

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Keywords: Diazo compounds • azide • dihydroindole • C–H insertion • rhodium

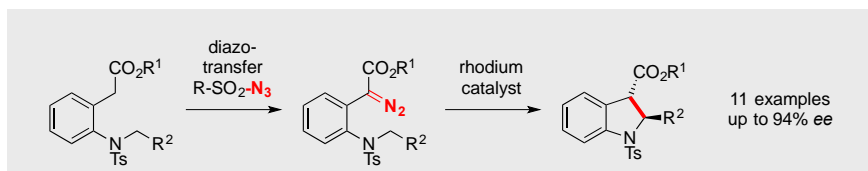
- [1] a) H. Ishikawa, D. A. Colby, S. Seto, P. Va, A. Tam, H. Kakei, T. J. Rayl, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* **2009**, *131*, 4904-4916; b) S. Yokoshima, H. Tokuyama, T. Fukuyama, *Chem. Rec.* **2010**, *10*, 101-118.
- [2] a) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758-8759; b) G. Pandey, J. Khamrai, A. Mishra, *Org. Lett.* **2015**, *17*, 952-955.
- [3] A. Rakhit, M. E. Hurley, V. Tipnis, J. Coleman, A. Rommel, H. R. Brunner, *J. Clin. Pharmacol.* **1986**, *26*, 156-164.
- [4] a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131; b) J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525-7546; c) B. H. Yang, S. L. Buchwald, *Org. Lett.* **1999**, *1*, 35-38.
- [5] J. N. Johnston, M. A. Plotkin, R. Viswanathan, E. N. Prabhakaran, *Org. Lett.* **2001**, *3*, 1009-1011.
- [6] a) D. W. Zhang, L. S. Liebeskind, *J. Org. Chem.* **1996**, *61*, 2594-2595; b) W. F. Bailey, X. L. Jiang, *J. Org. Chem.* **1996**, *61*, 2596-2597; c) S. Anas, H. B. Kagan, *Tetrahedron: Asymmetry* **2009**, *20*, 2193-2199; d) D. Liu, G. Zhao, L. Xiang, *Eur. J. Org. Chem.* **2010**, 3975-3982.
- [7] E. Ascic, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 4666-4669.
- [8] H. M. L. Davies, M. V. A. Grazini, E. Aouad, *Org. Lett.* **2001**, *3*, 1475-1477.
- [9] H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, S. Hashimoto, *Org. Lett.* **2002**, *4*, 3887-3890.
- [10] R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 3437-3440.
- [11] G. Maas, *Angew. Chem. Int. Ed.* **2009**, *48*, 8186-8195.
- [12] a) S. M. Nicolle, W. Lewis, C. J. Hayes, C. J. Moody, *Angew. Chem. Int. Ed.* **2016**, *55*, 3749-3753; b) M. Peña-López, M. Beller, *Angew. Chem. Int. Ed.* **2017**, *56*, 46-48.
- [13] a) T. Ye, M. A. McKevey, *Chem. Rev.* **1994**, *94*, 1091-1160; b) M. P. Doyle, M. A. McKevey, T. Ye, in *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**; c) H. M. L. Davies, A. M. Walji in *Modern Rhodium-Catalyzed Organic Reactions*, Wiley-VCH, Weinheim, **2005**, pp. 301-340.
- [14] a) S. Lee, H.-J. Lim, K. L. Cha, G. A. Sulikowski, *Tetrahedron* **1997**, *53*, 16521-16532; b) G. Sulikowski, S. Lee, *Tetrahedron Lett.* **1999**, *40*, 8035-8038.
- [15] a) H. M. L. Davies, W. R. Cantrell, K. R. Romines, J. S. Baum, *Org. Synth.* **1991**, *70*, 93; b) H. M. L. Davies, M. V. A. Grazini, E. Aouad, *Org. Lett.* **2001**, *3*, 1475-1477; c) D. F. Taber, R. B. Sheth, P. V. Josh, *J. Org. Chem.* **2005**, *70*, 2851-2854.
- [16] a) S. T. R. Müller, A. Murat, D. Maillos, P. Lesimple, P. Hellier, T. Wirth, *Chem. Eur. J.* **2015**, *21*, 7016-7020; b) S. T. R. Müller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Chem.* **2016**, *20*, 495-502.
- [17] CCDC-1441276 (**3a**), CCDC-1441277 (**4a**) and CCDC-1441275 (**9a**) contain 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.
- [18] M. Regitz, *Angew. Chem. Int. Ed.* **1966**, *5*, 681-682.

[19] a) M. Schroen, S. Bräse, *Tetrahedron* **2005**, *61*, 12186-12192; b) E. L. Myers, R. T. Raines, *Angew. Chem. Int. Ed.* **2009**, *48*, 2359-2363.

[20] D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

Entry for the Table of Contents

COMMUNICATION



Azides vs. Diazos: The competition in the diazo-transfer was resolved which allowed the development of a highly selective synthesis of *trans*-indolines.

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