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Intramolecular Michael Reaction of *tert*-Butylsulfinyl Ketimines: Asymmetric Synthesis of 3-Substituted Indanones

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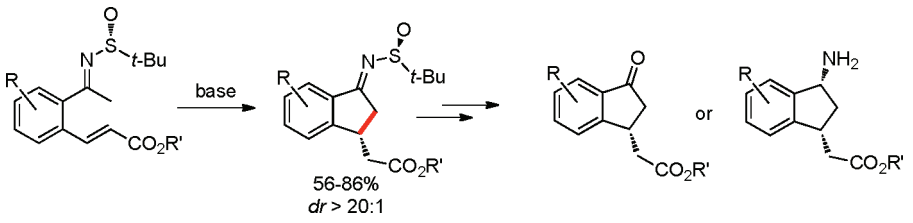
ABSTRACT



Aromatic *tert*-butylsulfinyl ketimines bearing a suitable Michael acceptor at the *ortho* position readily undergo an intramolecular conjugate addition achieving indanone derivatives in good yields and complete diastereoselectivity.

The indane core, and specifically the indanone subunit, is a common skeleton in both natural products and synthetic drugs.[1,2] In recent years, several approaches for the asymmetric construction of the indanone skeleton have been reported.[3,4] Among them, the hydroacylation of *o*-formylstyrenes **I** (arising from the C1−C2 disconnection) developed by Morehead[3b] and the isomerization of α-arylpropargyl alcohols **II** (arising from the C3−C4 disconnection) followed by cyclization reported by Hayashi[3c] deserve special mention (Scheme 1).

The alternative disconnection C2−C3 would lead to readily available *o*-functionalized acetophenone derivatives **III**. Despite its simplicity, the asymmetric variant of this intramolecular Michael reaction has so far not been reported,[5] to the best of our knowledge. Moreover, the intramolecular version of the asymmetric Michael reaction is notably less developed than its intermolecular counterpart.[6]

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(1) For some representative natural products, see: (a) Boland, W.; Hopke, J.; Donath, J.; Nüske, J.; Bublitz, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1600. (b) Nagle, D. G.; Zhou, Y.-D.; Park, P. U.; Paul, V. J.; Rajbhandari, I.; Duncan, C. J. G. *J. Nat. Prod.* **2000**, *63*, 1431. (c) Okpekon, T.; Millot, M.; Champy, P.; Gleye, C.; Yolou, S.; Bories, C.; Loiseau, P.; Laurens, A.; Hocquemiller, R. *Nat. Prod. Res.* **2009**, *23*, 909.

(2) For some pharmaceutically relevant products, see: (a) Kobayashi, A.; Egawa, H.; Koshimizu, K.; Mitsui, T. *Agric. Biol. Chem.* **1975**, *39*, 1851. (b) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (c) Omran, Z.; Cailly, T.; Lescot, E.; Santos, J. S. D.; Agondanou, J. H.; Lisowski, V.; Fabis, F.; Godard, A. M.; Stiebing, S.; Le Flem, G.; Boulouard, M.; Dauphin, F.; Dallemagne, P.; Rault, S. *Eur. J. Med. Chem.* **2005**, *40*, 1222. (d) Elati, C. R.; Kolla, N.; Chalamala, S. R.; Vankawala, P. J.; Sundaram, V.; Vurimidi, H.; Mathad, V. T. *Synth. Commun.* **2006**, *36*, 169.

(3) For methodologies based on transition metal catalysis, see: (a) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380. (b) Kundu, K.; McCullagh, J. V.; Morehead, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (c) Shintani, R.; Yashio, K.; Nakamura, T.; Okamoto, K.; Shimada, T.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2772. (d) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2005**, *8*, 3379. (e) Seiser, T.; Cathomen, G.; Cramer, N. *Synlett* **2010**, 1699. (f) Brekan, J. A.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 1472. (g) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 10163.

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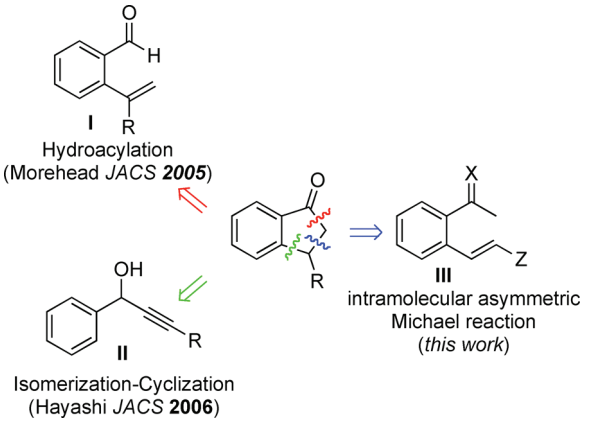
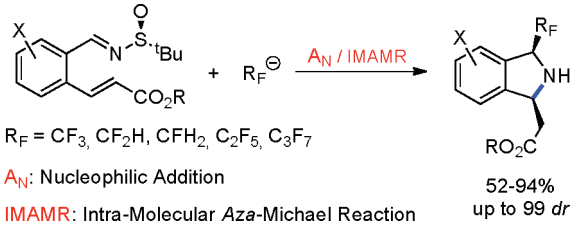
Scheme 1. Methods for the Asymmetric Construction of the Indanone Ring



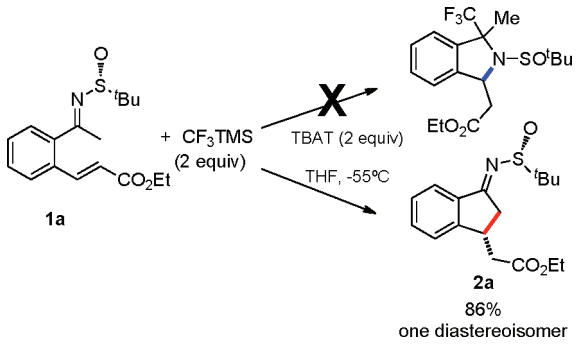
In a recent report, we described a new nucleophilic addition (A_N)/Intramolecular *Aza*-Michael Reaction (IMAMR) tandem process for the stereoselective synthesis of 1,3-disubstituted fluorinated isoindolines (Scheme 2).[7] For this aim, we used *o*-functionalized *tert*-butanesulfinyl[8] aldimines analogous to **III**.

Scheme 2. Tandem A_N/IMAMR for the Asymmetric Synthesis of Fluorinated Isoindolines



Complementary to this work, we decided to study the reactivity of the corresponding ketimines toward the Ruppert–Prakash reagent (CF_3TMS)[9] targeting 1,3-disubstituted isoindolines featuring a quaternary stereocenter. When model substrate **1a** was subjected to the optimized conditions obtained for the tandem A_N/IMAMR with aldimines, the formation of the expected isoindoline remained unobserved.[10] Instead the only isolated product was the indanone derivative **2a** arising from an intramolecular Michael reaction through the imine α-position without incorporation of the CF_3 moiety. Moreover, **2a** is afforded in good yield and as a single diastereoisomer, as judged by ^1H NMR (Scheme 3).

Scheme 3. Preliminary Result Regarding the Reactivity of **1a** towards CF_3TMS



The difference in reactivity between aldimines and ketimines can be rationalized by a double effect: first, the inherent lower reactivity of ketimines toward nucleophiles such as CF_3TMS is due to their diminished electrophilicity together with a higher steric bulk;[11] second, acidic protons are present at the α-position, providing an alternative reaction pathway. Thus, the "CF_3^-" anion formed upon mixing the Ruppert–Prakash reagent with a fluorine source acts as a base,[12] while in the case of aldimines it behaves as a nucleophile.[13] In fact, the addition of fluoroalkyl carbanions was unprecedented until very recently.[10] Only the use of stabilized carbanions, derived from fluoro- or difluoromethyl phenylsulfone, is effective in the fluoroalkylation of ketimines. The presence of the sulfone group renders a less basic carbanion. The balance between nucleophilicity and basicity may account for the different behavior.

In order to establish the relative configuration of the new stereocenter by X-ray analysis, suitable crystals of **2a** were obtained (Figure 1).[14] Thus, the relative stereochemistry of the newly created stereocenter in **2a** was established to be *R*.

(6) Reports in this context are practically limited to organocatalytic processes; for some recent examples, see: (a) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (b) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (c) Kikuchi, M.; Inagaki, T.; Nishiyama, H. *Synlett* **2007**, 1075. (d) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107.

(7) Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Rodríguez, E.; Barrio, P. *Org. Lett.* **2010**, *12*, 5494.

(8) For an exhaustive review on the use of this chiral auxiliary in asymmetric synthesis, see: Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(9) (a) Krishnamurti, R.; Bellew, B. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (c) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.

(10) A small amount *ca.* 5% of the corresponding isoindoline was obtained along with the major reaction product.

(11) The addition of fluoroalkyl anions to ketimines was reportedly hampered; see: (a) Liu, J.; Zhang, L.; Hu, J. *Org. Lett.* **2008**, *10*, 5377. (b) Liu, J.; Hu, J. *Chem.—Eur. J.* **2010**, *16*, 11443.

(12) To the best of our knowledge, the combination CF_3TMS/fluoride source (i.e., TBAT: tetrabutylammonium difluorotriphenylsilicate) has never been reported as a base.

(13) Control experiments with either reagent (CF_3TMS or TBAT) have been carried out separately. In both cases unaltered starting materials were recovered, even after several hours at room temperature.

(14) For details, see Supporting Information.

(15) This transition state has been suggested according to the most stable conformation of the corresponding enamine, which was in turn obtained by an MM2 minimization. A stabilizing electrostatic interaction between the oxygen of the sulfinamide and the electrophilic ester carbonyl carbon leading to a rigid eight-membered boat-like transition state could explain the high diastereoselectivities observed. For similar eight-membered transition states in intramolecular Michael reactions, see ref 4.

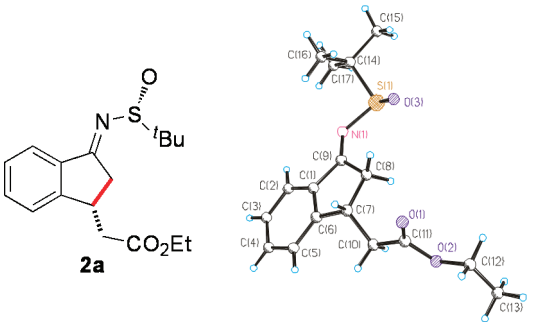


Figure 1. ORTEP diagram for **2a**.

To explain the stereochemical outcome observed for this transformation, we proposed the following transition state (Figure 2).[15]

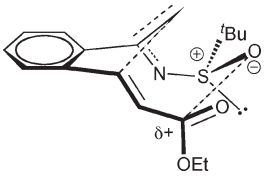


Figure 2. Proposed transition state.

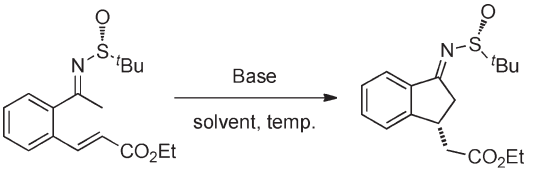
Given the interest of this unprecedented transformation, we decided to perform an optimization of the reaction conditions (Table 1).

Interestingly, the use of some common bases for enolate formation such as LiHMDS, NaHMDS, LDA, or ^{t}BuOK led to significant lower yields than the combination CF_3TMS/TBAT (Table 1, entries 2–5) even after temperature optimization for each base. For the base leading to the best results, namely LiHMDS, a solvent screening was carried out but no beneficial effect was obtained (Table 1, entries 6, 7). Finally, among the fluoride sources only the most basic TBAF is able to promote the transformation on its own (Table 1, entry 8), although in comparable yield with the initial conditions (CF_3TMS/TBAT). Thus, we have found two sets of reaction conditions leading to the asymmetric intramolecular Michael addition in good yield and diastereoselectivity: CF_3TMS/TBAT, THF, −55 to −20 °C and TBAF, THF, −55 to −20 °C (Table 1, entries 1 and 8).[16]

With these optimized reaction conditions in hand, we turned to evaluate the scope of the transformation (Table 2).

The reaction showed broad scope with regard to the substitution on the aromatic ring as well as the ester group. In all cases, despite the electronic character of the aromatic ring or the steric bulk at the ester moiety the yields were moderate to high and, remarkably, complete diastereocontrol was observed (Table 2).

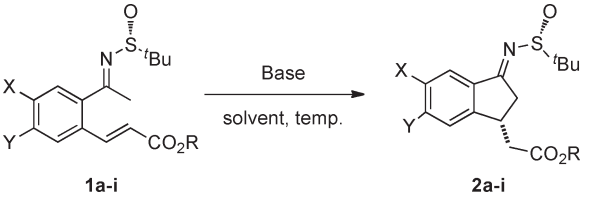
Table 1. Optimization of the Reaction Conditions



entry	base	solv	temp (°C)	yield (%)	*dr*
1	CF_3TMS/TBAT[a]	THF	−55 to −20	86	>20:1
2	LiHMDS	THF	−78 to rt	65	>20:1
3	NaHMDS	THF	−78 to −20	46	>20:1
4	LDA	THF	−78 to rt	33	>20:1
5	^{t}BuOK	THF	0	20	>20:1
6	LiHMDS	DCM	−78 to −20	30	>20:1
7	LiHMDS	Tol-H	−78 to −20	36	>20:1
8	TBAF	THF	−55 to −20	76	>20:1
9	CsF	THF	−55 to −20	SM	–

[a] The use of fluoride sources other than TBAT (i.e., TBAF or CsF) proved to be less efficient.

Table 2. Reaction Scope



entry	X	Y	R	product	yield (%)[a]	*dr*
1	H	H	Et	**2a**	86 (76)	>20:1
2	MeO	H	Et	**2b**	52 (65)	>20:1
3	CF_3	H	Et	**2c**	63 (61)	>20:1
4	F	H	Et	**2d**	70 (80)	>20:1
5	O-CH_2-O		Et	**2e**	64 (54)	>20:1
6	H	Me	Et	**2f**	63 (82)	>20:1
7	H	H	^{t}Bu	**2g**	73 (88)	>20:1
8	H	H	Bn	**2h**	73	>20:1
9	H	H	^{i}Pr	**2i**	72 (82)	>20:1

[a] Yields in parentheses refer to reactions performed with TBAF (1.2 equiv).

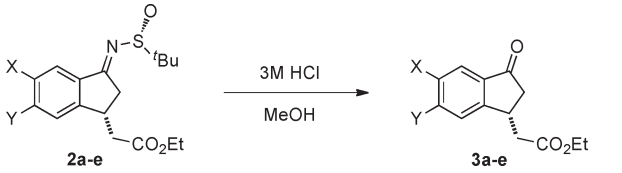
(16) In an attempt to rationalize the performance of these uncommon bases, we suggest that the bulky noncoordinating tetrabutyl ammonium cation leads to a more reactive "metaloenamine" intermediate than the corresponding metal cation which could be stabilized by the negatively charged oxygen of the chiral sulfoxide group *via* a six-membered chelate.

(17) Liu, Z.-J.; Mei, Y.-Q.; Liu, J.-T. *Tetrahedron* **2006**, *63*, 855.

(18) For details, see Supporting Information.

At this stage, the hydrolysis of the chiral auxiliary affords asymmetric 3-substituted indanones, a challenging structural motif. This was achieved by using the conditions reported by Liu et al. (Table 3).[17] From this table, we can conclude that, in most cases, epimerization does not take place to a noticeable extent. The enantiomeric excesses obtained (86−96% ee) are, in all cases, comparable to those reported by Morehead[3b] and Hayashi.[3c]

Table 3. Removal of the Chiral Auxiliary



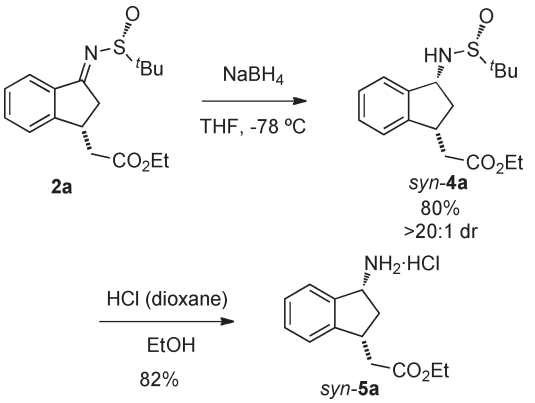
entry	X	Y	product	yield (%)	*ee* (%)[a]
1	H	H	**3a**	53	93
2	MeO	H	**3b**	56	94
3	CF_3	H	**3c**	67	86
4	F	H	**3d**	46	96
5	O-CH_2-O		**3e**	62	94

[a] Determined by HPLC on chiral stationary phase using a Chiralcel OD-H column (see ref 18).

In order to expand the synthetical utility of our methodology, we carried out the chemoselective reduction of the imino group giving rise to δ-amino acid derivatives.[19] Under the first conditions essayed ($NaBH_4$, MeOH, 0 °C), a modest 5:1 *dr* was achieved. This result could be significantly improved by changing the reaction conditions to wet THF at −78 °C. Under these new conditions, only one diastereoisomer was observed in the ^1H NMR spectrum of the crude reaction (Scheme 4).[20]

δ-Amino acid derivative *syn*-**4a**[21] can thus be stereoselectively achieved.[22] Furthermore, the chiral auxiliary has in turn been removed[23] affording the free NH_2 δ-amino ester *syn*-**5a** in 82% yield as the hydrochloride salt.

Scheme 4. Chemoselective Reduction Leading to δ-Amino Acid Derivatives



In conclusion, we have developed a new intramolecular asymmetric Michael reaction of *tert*-butanesulfinyl ketimines for the diastereoselective synthesis of indanone derivatives. The products have been obtained in good yields and excellent diastereoselectivity. Remarkably, this transformation is carried out more easily with nonobvious bases such as CF_3TMS/TBAT or TBAF. Indanones can be obtained in high yields and optical purity by hydrolysis. On the other hand, the diastereoselective reduction of the sulfinime allows δ-amino acid derivatives to be afforded. Further applications of this methodology are currently being studied in our laboratories.

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Supporting Information Available. Experimental procedures and NMR spectra for all new compounds, as well as crystallographical data for compound **2a**, including its CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) For the use of δ-amino acids in the synthesis of β-turn containing peptide hairpins, see: Rai, R.; Vasudev, P. G.; Ananda, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem.—Eur. J.* **2007**, *13*, 5917.

(20) We also essayed the diastereodivergent reduction using L-selectride as the reducing agent, but low yields (30%) and diastereoselectivities (5:1 *dr*) were achieved. The reversal diastereofacial selectivity in the reductions of *tert*-butylsulfinilketimines by either $NaBH_4$ or L-selectride has been described: Colyer, J. T.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859.

(21) A cross-peak between the two methine protons in the NOESY spectrum of **4a** allowed assignment of the relative stereochemistry of the new stereocenter. The stereochemical outcome is in agreement with the chelated transition state suggested for reductions of *tert*-butanesulfinimides with $NaBH_4$ (see Supporting Information).

(22) For recent diastereoselective syntheses of δ-amino acids, see: (a) Sünnemann, H. W.; Hofmeister, A.; Magull, J.; de Meijere, A. *Chem.—Eur. J.* **2006**, *12*, 8336. (b) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687.

(23) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.