Organocatalysis

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Enantioselective Phase-Transfer Catalysis: Synthesis of Pyrazolines**

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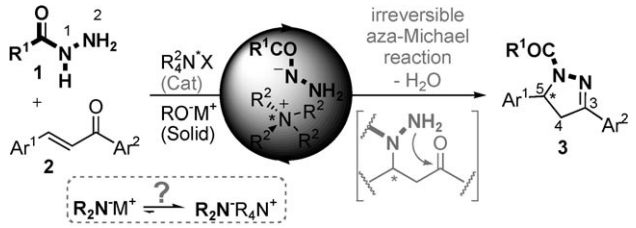
The development of asymmetric catalytic reactions, as cost-effective and environmentally friendly methodologies, is a response to the increased demand of pharmaceutically relevant chiral aza-heterocycles.[1] In this context, the Δ^2-pyrazolinyl platform is the core structure of many bioactive ingredients, and among them are the recurring 3,5-diaryl-pyrazoline architectures **3** (Scheme 1),[2] which have a polar group on N1.[3] However, an efficient enantioselective synthesis of this type of 4,5-dihydropyrazoles remains elusive.



Scheme 1. Organocatalytic strategy using chiral ammonium/amide ion pairs.

The first catalytic enantioselective construction of pyrazolines, which was reported in 2000, proceeds through 1,3-dipolar cycloaddition reactions of acrylamides by means of Lewis acidic magnesium complexes.[4] The subsequently developed asymmetric approaches were dominated by organometallic strategies which encompass [2+3] cycloadditions of either diazoalkane dipoles[5] or nitrile imine dipole precursors, as well as others.[6,7] Alternatively, Kanemasa and Yanagita described a metal-promoted aza-Michael cyclocondensation cascade using electron-rich *N*-arylhydrazines to give exclusively 3-pyridyl-4-aryl pyrazolines, albeit with moderate enantioselectivity.[8] This example, to our knowledge, constitutes the only attempt to construct nonracemic 3,5-diaryl pyrazolines. The organocatalytic asymmetric synthesis of *N*-aryl pyrazolines was pioneered by List and Müller by making use of an elegant 6 π electrocyclization.[9] This recent achievement paves the way for the development of original transition-metal-free synthetic strategies that are suited to the elaboration of pharmaceutically relevant chiral heterocycles.

To provide efficient access to the chiral nonracemic 3,5-diarylpyrazoline **3** (Scheme 1), bearing a polar group on N1 [usually an electron-withdrawing group (EWG)], we envisaged a domino aza-Michael addition/cyclocondensation reaction of electron-poor hydrazine anions with chalcones catalyzed by a chiral quaternary ammonium salt.[10] We assumed that an irreversible (nonracemizing) conjugate addition of deprotonated acylhydrazines would be secured by the subsequent imine bond formation.[11] However, the formation of an effective chiral ion pair between an amide anion and an ammonium salt through cation exchange (M^+/R_4N^+) remained questionable, but was required to prevent a racemic background process. Thus far, phase-transfer catalysis (PTC) has elicited robust organocatalytic strategies for the asymmetric construction of C–C bonds from C anions and, to a lesser extent, C–X bonds from anionic O and S nucleophiles.[12] Nonetheless, the examples of asymmetric PTC approaches for C–N bond formation using anionic N-nucleophilic species are rare.[10,12,13] In the 1970s, Juliá et al. pioneered the kinetic resolution of chiral tertiary alkyl bromides by using potassium phthalimide nucleophiles under the influence of cinchonium-derived alkaloids albeit with modest selectivities.[14] Later in 1996, preliminary investigations from Prabhakar and co-workers triggered a series of studies dealing with the asymmetric aziridination reactions of enones by O-substituted hydroxylamide anions,[15a–d] and then later extended to *N*-chloro-*N*-sodio carbamate.[15e] Recently, a useful intramolecular enantioselective conjugate addition of deprotonated indoles to an acrylate was achieved under PTC conditions.[16] We describe herein an unprecedented asymmetric synthesis of pyrazolines under PTC reaction conditions by making use of the R_2N^-/R_4N^+ ion pairing mode of activation.[17]

We first carried out a set of reactions between chalcone (**2a**) and *N*-*tert*-butyloxycarbonyl hydrazine **1a** (1.1 equiv) in the presence of potassium carbonate (solid–liquid phase-transfer conditions) and various commercially or easily available chiral ammonium salts derived from cheap cinchona alkaloids (Table 1).[12c] Pleasingly, 10 mol% of *N*-benzyl quininium **4a** furnished (*S*)-(−)-pyrazoline **3a** with a promising 67% *ee* albeit in 31% yield. Subsequent attempts revealed that the presence of water (liquid–liquid phase-transfer conditions with **4a**; Table 1 < xtabr1, entry 2) and the use of cinchonidinium salt **4b** were detrimental to the enantiomeric excess. Interestingly, the introduction of an

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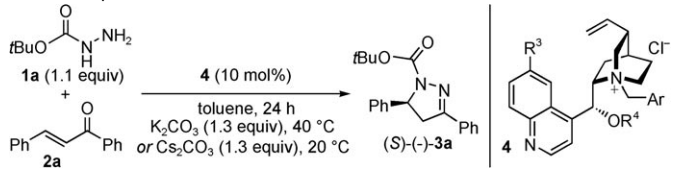
Table 1: Optimization of the reaction.



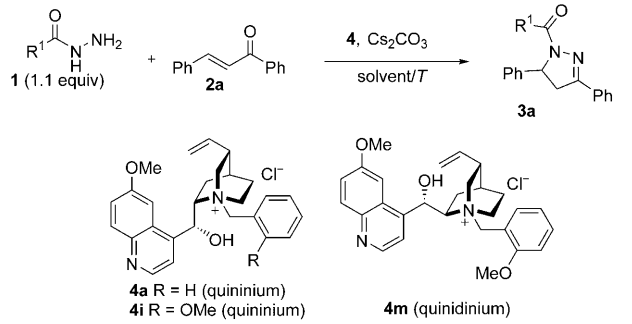
Entry	4	R^3	R^4	Ar	Base/T [°C]	Yield [%][a]	*ee* [%][b]
1	**4a**	OMe	H	Ph	K_2CO_3/40	31	67
2	**4a**	OMe	H	Ph	K_2CO_3/40	20[c]	57
3	**4b**	H	H	Ph	K_2CO_3/40	11	48
4	**4c**	OMe	allyl	Ph	K_2CO_3/40	17	20 (*R*)[d]
5	**4a**	OMe	H	Ph	Cs_2CO_3/20	55	73
6	**4d**	OMe	H	anthracenyl	Cs_2CO_3/20	15	12 (*R*)[d]
7	**4e**	OMe	H	4-$MeOC_6H_4$	Cs_2CO_3/20	58	56
8	**4f**	OMe	H	4-$CF_3C_6H_4$	Cs_2CO_3/20	38	54
9	**4g**	OMe	H	4-FC_6H_4	Cs_2CO_3/20	46	61
10	**4h**	OMe	H	2-FC_6H_4	Cs_2CO_3/20	72	79
11	**4i**	OMe	H	2-$MeOC_6H_4$	Cs_2CO_3/20	80	80
12	**4j**	OMe	H	2-MeC_6H_4	Cs_2CO_3/20	54	68
13	**4k**	OMe	H	2-pyridyl	Cs_2CO_3/20	48	24
14	**4l**	OMe	H	2-pyridyl-*N*-oxide	Cs_2CO_3/20	84	65

[a] Yield of pyrazine **3a** determined by NMR methods using an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Toluene/H_2O (75:25) used as solvent. [d] Absolute configuration determined by comparison to analogue **6a**; see Ref. [21].

allylic functional group on the alcohol at C9 (**4c**) or using the bulkier anthracenyl derivative **4d** led to an reversal of the enantioselectivity and low-yielding reactions. Apparently, the suitable organization of the amide/ammonium ion pair that leads to efficient chirality transfer during the C–N bond formation requires the presence of a free alcohol at C9. Futhermore, the steric hindrance at the benzylic moiety of the quinuclidinium structure appeared to be a limiting structural feature as exemplified by the catalyst **4d**. At this stage, it was found that the use of cesium carbonate instead of potassium carbonate improved the yields (from 31% to 55% for catalyst **4a**) while allowing the lowering of the reaction temperature from 40°C to 20°C (67% to 73% *ee* for catalyst **4a**). Then, we turned our attention to electronic effects and tested catalysts having *para*-substituted benzylic rings (**4e**–**4g**), but disappointing results were obtained. Recently, Jew, Park, and coworkers pioneered *ortho*-substituted benzyl cinchona derivatives such as **4h** as potent catalysts for glycine alkylation.[18] Such catalysts were successfully exploited by Ricci and coworkers, who used *ortho*-methoxy benzyl ammonium salts such as **4i** in several elegant PTC processes.[19] In our hands, the enantiomeric excesses were improved from 73% *ee* with quininium **4a** to 79% *ee* with *ortho*-fluorobenzyl compound **4h**, and a faster reaction was achieved such that pyrazoline **3a** was isolated in 72% yield after 24 hours. The best results (80% *ee*) were obtained with quininium salt **4i**, which possesses a free alcohol and an *ortho*-methoxybenzyl motif. In this regard, structure–activity relationships were examined and revealed that the 2-methyl-substituted catalyst **4j** furnished only 68% *ee*, thereby excluding a simple steric influence on selectivity. The comparison of the activity between the 2-pyridyl **4k** and 2-pyridyl-*N*-oxide **4l** derivatives shows that a polar functional group at the *ortho* position of the benzylic substructure is required; this polar group (e.g., *N*-oxide) is likely to accept hydrogen bonds which in turn results in improved yields and *ee* values. Nevertheless, catalysts **4k** and **4l** containing a pyridine ring resulted in a less enantioselective reaction (see the Supporting Information for further details).[18]

To investigate the scope of the reaction, we examined the EWG on the hydrazine ($R^1CONHNH_2$) in the presence of catalyst **4a** (Table 2). Although the *N*-benzoyl hydrazine

Table 2: Optimization with various hydrazines $R^1CONHNH_2$ **1**.[a]



Entry	Cat.	R^1	Solvent/*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**4a**	Ph	toluene/RT	0	–
2	**4a**	Me	toluene/RT	86	9
3	**4a**	OEt	toluene/RT	74	26
4	**4a**	OBn	toluene/RT	60	26
5	**4a**	O*t*Bu	toluene/RT	55	73 (*S*)
6	**4a**	O*t*Bu	toluene/0	55	78 (*S*)
7	**4a**	O*t*Bu	toluene/−20	45	23 (*S*)
8	**4i**	O*t*Bu	THF/0	80	92 (*S*)
9	**4m**	O*t*Bu	THF/0	78	92 (*R*)
10[d]	**4i**	O*t*Bu	THF/0	77	93 (*S*)[e]

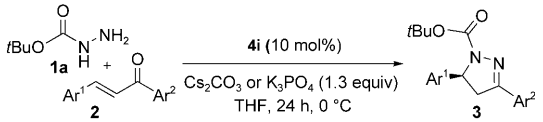
[a] Reaction conditions: chalcone **2a** (0.5 mmol), hydrazine **1** (1.1 equiv), Cs_2CO_3 (1.3 equiv), and 10 mol% of catalyst **4** for 24 h. [b] Yield of pyrazoline **3a** determined by NMR methods using an internal standard. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Carried out with chalcone **2a** (2 mmol), 2 mol% of catalyst **4i** and 0.5 equivalents of Cs_2CO_3 for 87 h giving 70% yield of the isolated product after column chromatography (43% yield in 24 h). [e] Greater than 99% *ee* after one recrystallization in EtOAc/petroleum ether (1:3). Bn = benzyl.

(Table 2, entry 1) did not yield the pyrazoline product **3a**, the *N*-acetyl derivative (Table 2, entry 2) smoothly reacted with chalcone **2a** to give the corresponding pyrazoline in 86% yield, but low selectivity was measured. The bulky *N*-Boc hydrazine was the only carbamate derivative (Table 2, entries 3–5) to achieve a significant *ee* value in its reaction, thereby showing the subtle influence of both the steric hindrance and pK_a value of the hydrazine nucleophiles upon these asymmetric aza-Michael reactions. The enantiomeric excesses were slightly improved at 0°C (Table 2, entry 6), but a lower temperature was detrimental to the reaction (Table 2, entry 7). Consequently, by using the more competent *ortho*-methoxy quininium catalyst **4i** (see the Supporting Information) in THF at 0°C, the efficient formation of pyrazoline **3a** was observed in 80% yield with 92% *ee* (Table 2, entry 8).

Most importantly, the pseudo-enantiomeric effect was fully countered by means of using 10% of the quinidinium catalyst **4m** (Table 2, entry 9), which allowed the construction of (*R*)-**3a**. We also demonstrated that on a 2 mmol scale only 0.5 equivalents of Cs_2CO_3 and 2 mol% of catalyst **4i** (Table 2, entry 10) were needed to maintain the high enantioselectivity (93% *ee*), but the reaction required 87 hours to reach completion. As a practical issue for the synthesis of chiral drugs, a virtually enantiopure pyrazoline **3a** could be obtained after one recrystallization (Table 2, entry 10).

We evaluated these user-friendly and cost-effective organocatalytic conditions by applying them to reactions of chalcone derivatives (**2**) with a quasi-stoichiometric amount of **1a** (Table 3). Pyrazolines **3** having various aryl (Table 3, entries 1–6 and 9) and heterocyclic (Table 3, entries 7 and 8) substituents at C3 were formed with more than 90% *ee*. As a general trend, it was found that K_3PO_4 slightly improved the enantiomeric excesses relative to those obtained with Cs_2CO_3 (Table 3, entries 4, 6, and 8), but the reactions were slower and the yields were lower after the same reaction time (24 hours). The *ortho, meta,* and *para* substitution on the aryl rings at C5 were well tolerated even though a slight drop in the *ee* values was measured (Table 3, entries 10–13). The thienyl heterocycle led to a lower enantiomeric excess (Table 3, entry 14).[20]

Table 3: Scope of the enantioselective synthesis of pyrazolines.[a]

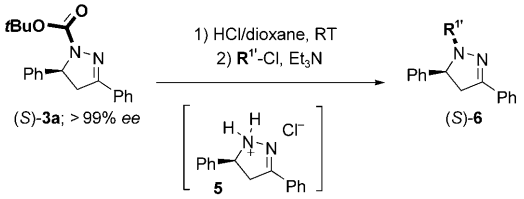


Entry	Base	Ar^1	Ar^2	Yield [%][b]	*ee* [%][c]
1	Cs_2CO_3	Ph	Ph	77	92 (−)
2	Cs_2CO_3	Ph	4-$MeOC_6H_4$	71	90 (−)
3	Cs_2CO_3	Ph	4-FC_6H_4	72	90 (−)
4	K_3PO_4	Ph	4-FC_6H_4	62	92 (−)
5	Cs_2CO_3	Ph	2-$MeOC_6H_4$	89	92 (−)
6	K_3PO_4	Ph	2-$MeOC_6H_4$	52	94 (−)
7	Cs_2CO_3	Ph	2-thienyl	66	87 (−)
8	K_3PO_4	Ph	2-thienyl	60	91 (−)
9	K_3PO_4	Ph	3,4-ClC_6H_3	40 (62)[d]	92 (−)
10	K_3PO_4	4-$MeOC_6H_4$	Ph	60	89 (+)
11	K_3PO_4	4-ClC_6H_4	Ph	70	88 (−)
12	K_3PO_4	2-MeC_6H_4	Ph	62	89 (−)
13	K_3PO_4	3-$MeOC_6H_4$	Ph	61	91 (−)
14	K_3PO_4	2-thienyl	Ph	46	78 (−)

[a] Reactions were performed on a 0.5 mmol scale of chalcones **1** with 1.1 equivalent of hydrazine **1a**. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Yield determined by NMR analysis of the crude reaction mixture using an internal standard.

The use of **1a** was key to the success of this enantioselective synthesis of the 3,5-diaryl pyrazolines, but the methodology is restricted to the formation of *N*-Boc derivatives. Nevertheless, we achieved a practical one-pot protecting-group exchange by making use of the acid lability of the *N*-Boc group, thereby extending the scope of this methodology (Table 4). A straightforward construction of **6a–c** (Table 4, entries 1–3) and diastereoisomeric **6d** (Table 4, entry 4) was realized, without any racemization, starting from the enantioenriched pyrazoline **3a** (see Table 2, entry 10). Considering the usual chemical and configurational instability of 1*H*-pyrazolines through oxidative degradation pathways,[11] this achievement is noteworthy. The formation of an ammonium intermediate **5** is likely and prevents any decomposition. Pleasingly, the resulting product **6a** (Table 4, entry 1) was crystalline and the absolute configuration at C5 of the pyrazoline ring was determined to be *S* as confirmed by X-ray diffraction methods.[21]

Table 4: One-pot protecting-group exchange.



Entry	Product	$R^{1'}$	Yield [%][a]	Selectivity[b]
1	**6a**	Ts	86	> 99% *ee* (−)
2	**6b**	Ac	99	> 99% *ee* (−)
3	**6c**	Bz	99	> 99% *ee* (−)
4	**6d**	camphor sulfonyl	93	> 99% *de*[c]

[a] Yield of product isolated after column chromatography. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Determined by ^{1}H NMR analysis. Bz = benzoyl, Ts = 4-toluenesulfonyl.

With the *ortho*-fluorobenzyl ammonium catalyst **4h** Jew, Park, and co-workers demonstrated, by using X-ray crystal diffraction, that a molecule of water was bound between the oxygen atom on C9 and the *ortho*-fluorine atom on the benzyl moiety.[18] The authors proposed that preorganization of the obtained complex leads to improvement of the chiral induction. In our case, however, hydrated conditions yielded a drop in the *ee* values.[22] We suppose instead that both OH and OMe functional groups of quininium catalyst **4i** are synergistically involved in a hydrogen-bond network around the nucleophilic hydrazine anion of **1a**, thus providing a useful chiral platform for the selection of the prochiral enone faces en route to an effective asymmetric synthesis of pyrazolines (see the Supporting Information).[23] This hypothesis is currently under investigation.

In conclusion, we developed an original and straightforward enantioselective synthesis of 3,5-diaryl pyrazolines, biorelevant aza-heterocycles, by using phase-transfer organometallic methodology. The discovery that an *N*-*ortho*-methoxybenzyl quininium salt leads to a useful chiral ammonium/amide ion pair from *N*-acylhydrazines in this process has prompted investigations of its utility for other asymmetric transformations.

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[1] a) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337; b) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734.

[2] Reviews on pyrazolines: a) A. Lévai, *J. Heterocycl. Chem.* **2002**, *39*, 1; b) S. Kumar, S. Bawa, S. Drahu, R. Kumar, H. Gupta, *Recent Pat. Anti-Cancer Drug Discovery* **2009**, *4*, 154; c) M. Kissane, A. R. Maguire, *Chem. Soc. Rev.* **2010**, *39*, 845; d) C.-H. Küchenthal, W. Maison, *Synthesis* **2010**, *5*, 719.

[3] Representative bioactive 3,5-diarylpyrazolines: a) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi, D. M. Ferguson, *J. Med. Chem.* **2006**, *49*, 2127; b) P.-L. Zhao, F. Wang, M.-Z. Zhang, Z.-M. Liu, W. Huang, G.-F. Yang, *J. Agric. Food Chem.* **2008**, *56*, 10767; c) C. D. Cox, M. J. Breslin, B. J. Mariano, P. J. Coleman, C. A. Buser, E. S. Walsh, K. Hamilton, H. E. Huber, N. E. Kohl, M. Torrent, Y. Yan, L. C. Kuod, G. D. Hartman, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041; d) F. Chimenti, A. Bolasco, F. Manna, D. Secci, P. Chimenti, O. Befani, P. Turini, V. Giovannini, B. Mondovi, R. Cirilli, F. La Torre, *J. Med. Chem.* **2004**, *47*, 2071; e) A. Sahoo, S. Yabanoglu, B. N. Sinha, G. Ucar, A. Basu, V. Jayaprakash, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 132.

[4] S. Kanemasa, T. Kanai, *J. Am. Chem. Soc.* **2000**, *122*, 10710 and references cited therein for previous related diastereoselective methodologies. For preliminary discussions, see: K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863.

[5] [2+3] cycloadditions with diazoalkanes: a) T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2174; b) M. P. Sibi, L. M. Standley, T. Soeta, *Org. Lett.* **2007**, *9*, 1553; c) L. Gao, G.-S. Hwang, M. Y. Lee, D. H. Ryu, *Chem. Commun.* **2009**, 5460.

[6] [2+3] cycloadditions with nitrilimines: a) M. P. Sibi, L. M. Stanley, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 8276; b) M. P. Sibi, L. M. Standley, T. Soeta, *Adv. Synth. Catal.* **2006**, *348*, 2371.

[7] [2+3] cycloadditions of hydrazones: Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 11279.

[8] a) H. Yanagita, S. Kanemasa, *Heterocycles* **2007**, *71*, 699; b) for the first catalytic asymmetric aza-Michael reactions of hydrazines to afford pyrazolidinones, see: M. P. Sibi, T. Soeta, *J. Am. Chem. Soc.* **2007**, *129*, 4522. For an alternative use of hydrazones in aza-Michael reactions, see: c) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3565; d) S. Gogoi, C.-G. Zhao, D. Ding, *Org. Lett.* **2009**, *11*, 2249.

[9] S. Müller, B. List, *Angew. Chem.* **2009**, *121*, 10160; *Angew. Chem. Int. Ed.* **2009**, *48*, 9975.

[10] Review on organocatalytic aza-Michael reactions: a) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058; b) P. R. Krishna, A. Sreeshailam, R. Srinivas, *Tetrahedron* **2009**, *65*, 9657.

[11] For previous studies from our laboratory using guanidines in an aza-Michael mechanism for racemic products, see: O. Mahé, D. Frath, I. Dez, F. Marsais, V. Levacher, J.-F. Brière, *Org. Biomol. Chem.* **2009**, *7*, 3648, and references cited therein.

[12] Reviews on PTC: a) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; b) K. Maruoka, T. Hashimoto, *Chem. Rev.* **2007**, *107*, 5656; c) S.-S. Jew, H.-G. Park, *Chem. Commun.* **2009**, 7090.

[13] An example of alternative C–N bond formation with electrophilic amine reagents under PTC: R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466. For examples of racemic PTC aza-Michael reaction, see: a) L. W. Xu, L. Li, C.-G. Xia, S.-L. Zhou, J.-W. Li, X.-X. Hu, *Synlett* **2003**, 2337; b) J. Lee, M.-H. Kim, S.-S. Jew, H.-G. Park, B.-S. Jeong, *Chem. Commun.* **2008**, 1932; c) M. Ménard, V. Dalla, *Synlett* **2005**, 95.

[14] S. Juliá, A. Ginebreda, J. Guixer, A. Tomás, *Tetrahedron Lett.* **1980**, *21*, 3709, and references cited therein.

[15] a) J. Aires-de-Sousa, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **1996**, *37*, 3183; b) J. Aires-de-Sousa, S. Prabhakar, A. M. Lobo, A. M. Rosa, M. J. S. Gomes, M. C. Corvo, D. J. Williams, A. J. P. White, *Tetrahedron: Asymmetry* **2001**, *12*, 3349; c) R. Fioravanti, M. G. Mascia, L. Pellacani, P. A. Tardella, *Tetrahedron* **2004**, *60*, 8073; d) E. Murugan, A. Siva, *Synthesis* **2005**, *12*, 2022; e) S. Minakata, Y. Murakami, R. Tsuruoka, S. Kitanaka, M. Komatsu, *Chem. Commun.* **2008**, 6363. Except in reference [15c] the creation of a stereogenic center occurred during the ring-closing step of the aziridination reaction so that a chiral enolate/ammonium ion pair is involved during the stereoselective event instead of an amide/ammonium one.

[16] a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238.

[17] Selected review on organocatalysis: a) Special issue on organocatalysis: B. List, *Chem. Rev.* **2007**, *107*, 5413; b) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; c) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178, and references cited therein.

[18] M.-S. Yoo, B.-S. Jeong, J.-H. Lee, H.-G. Park, S.-S. Jew, *Org. Lett.* **2005**, *7*, 1129, and references cited therein.

[19] a) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338; b) R. D. Momo, F. Fini, L. Bernardi, A. Ricci, *Adv. Synth. Catal.* **2009**, *351*, 2283, and references cited therein.

[20] The present methodology did not furnish pyrazoline derivatives from aliphatic ketones. For instance, the *trans*-1-phenyl-2-buten-1-one mainly dimerized and gave a little of the aza-Michael product resulting from the conjugate addition of the primary amine of the *tert*-butylcarbazate. For precedent, see: F.-Y. Zhang, E.-J. Corey, *Org. Lett.* **2004**, *6*, 3397.

[21] CCDC 773701 contains the supplementary crystallographic data of pyrazoline (*S*)-(−)-**6a** 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. The absolute configurations of the remaining pyrazolines as *levo* (−) isomer were assigned (*S*) by analogy to **6a**. The only one exception to this rule is 5-(4-methoxyphenyl)-3-phenyl-pyrazoline (Table 2, entry 10).

[22] The *ortho*-fluorobenzyl catalyst **4h** with K_2CO_3 at 40 °C gave pyrazoline **3a** in 72 % *ee* in toluene and 57 % *ee* in a mixture of toluene/H_2O (75:25).

[23] For insight into role of the hydrogen bonds with ammonium PTC, see: E. Gomez-Bengoa, A. Linden, R. López, I. Múgica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955.

