ChemComm

A new benchmark for the non-enzymatic enantioselective acylation of amines: use of a planar-chiral derivative of 4-pyrrolidinopyridine as the acylating agent

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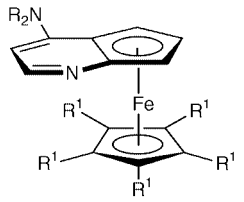
Received (in Corvallis, OR, USA) 27th October 1999, Accepted 23rd November 1999

_N_-Acetylated Ph-PPY*, a new planar-chiral derivative of PPY, serves as an effective reagent for the enantioselective acylation of racemic amines, providing amides with very good stereoselectivity.

In recent years substantial progress has been made in the development of non-enzymatic catalysts for the enantioselective acylation of alcohols.[1,2] In contrast, to the best of our knowledge there have been no reports of effective non-enzymatic catalysts for the enantioselective acylation of amines.[3,4] Indeed, there has been only limited success even with stoichiometric chiral acylating reagents.[5]

We have recently described applications of planar-chiral



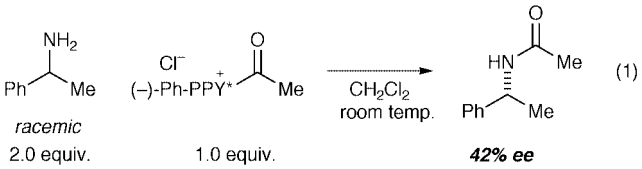
R^1 = Me, NR_2 = dimethylamino (–)-**1** (DMAP*)
R^1 = Me, NR_2 = pyrrolidino (–)-**2** (PPY*)
R^1 = Ph, NR_2 = dimethylamino (–)-**3** (Ph-DMAP*)
R^1 = Ph, NR_2 = pyrrolidino (–)-**4** (Ph-PPY*)

heterocycles (*e.g.* **1**–**3**) as nucleophilic catalysts for a variety of processes, including the enantioselective acylation of secondary alcohols.[6,7] Unfortunately, our attempts to extend this catalytic process to amines were frustrated by the facility with which amines react directly with acylating agents such as acetic anhydride, thereby providing a competitive, non-enantioselective pathway.

We therefore defined our immediate objective to be the development of a highly enantioselective stoichiometric reagent for the acylation of amines. Since progress toward this goal has been quite modest,[5] we felt that this in itself would be a worthwhile achievement.[8] Building on our recent discovery that planar-chiral Ph-DMAP* (**3**) undergoes *N*-acylation when treated with 1 equiv. of acetyl chloride,[2d] we examined the use of the acylated derivatives of iron complexes **1**–**4** as chiral reagents for the stereoselective acylation of (±)-1-phenylethylamine.

Our initial studies revealed that 4-pyrrolidino complexes provide higher ee than do 4-dimethylamino complexes and that complexes that bear the more bulky C_5Ph_5 group furnish better enantioselectivity than do those that bear the C_5Me_5 group. These cumulative substituent effects lead to the acylated form of a new planar-chiral PPY derivative (**4**; Ph-PPY*) being the most enantioselective acylating agent among complexes **1**–**4** [eqn. (1)].[9–11]

An optimization study established that the enantioselectivity with which acylated Ph-PPY* reacts with (±)-1-phenylethylamine varies with solvent. Although at room temperature several solvents furnish greater enantiomeric excess than does CH_2Cl_2 (Table 1), the stereoselection in CH_2Cl_2 is significantly



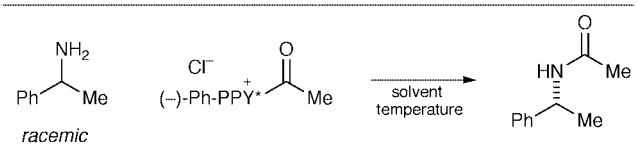
racemic 2.0 equiv. 1.0 equiv. 42% ee (1)

temperature-dependent, and acylation in CH_2Cl_2 at −78 °C affords the highest ee of the conditions that we have examined (78% ee; entry 3). Interestingly, the relationship between ee and solvent that we observe for the acylation of (±)-1-phenylethylamine differs from what we have observed for the catalytic asymmetric acylation of (±)-1-phenylethanol.[2b]

For enantioselective acylations of this sort, the ee of the amide product should increase when the ratio of amine to acylating agent is increased.[12] Consistent with this expectation, under otherwise identical conditions we obtain amide with 87% ee when we employ 8.0 equiv. of amine (Table 2, entry 1), compared with 78% ee when we use 2.0 equiv. of amine (Table 1, entry 3).

Under these reaction conditions, we can achieve the stereoselective acylation of a family of racemic amines with very good enantioselection (Table 2).[13] With respect to substituent effects, we observe somewhat lower ee as the steric demand of the alkyl substituent increases (entry 1 *vs.* entry 2). The stereoselectivity appears to be modestly dependent on the electronic nature of the aryl substituent, with acylations of (±)-1-phenylethylamine proceeding with higher enantioselection than either more electron-rich or more electron-poor derivatives (entry 1 *vs.* entries 3 and 4, respectively). As illustrated in Table 2, *N*-acylated Ph-PPY* efficiently differentiates the enantiomers of amines that bear a range of aromatic substituents (*e.g.* see entries 5 and 6).

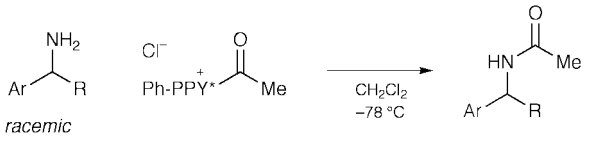
Table 1 Effect of solvent and temperature on enantioselectivity



racemic 2.0 equiv. 1.0 equiv.

		Ee of amide (%)	
Entry	Solvent	room temp.	−78 °C
1	Et_2O	17	30
2	THF	41	48
3	CH_2Cl_2	42	78
4	EtOH	44	45
5	Toluene	52	56
6	Pr^iOH	54	69
7	Acetone	58	66
8	*tert*-Amyl alcohol	66	——

Table 2 Enantioselective acylation of amines



Entry	Amine		Ee of amide (%)[a]
	Ar	R	
1	Ph	Me	87
2	Ph	Et	66
3	4-$MeOC_6H_4$	Me	81
4	4-$CF_3C_6H_4$	Me	85
5	1-Naphthyl	Me	90
6	2-MeC_6H_4	Me	91

[a] Average of two runs.

In summary, we have established that *N*-acylated Ph-PPY*, a new planar-chiral derivative of PPY, can serve as an effective reagent for the enantioselective acylation of racemic amines. Compared with other reagents that have been reported for this process, the level of stereoselectivity furnished by *N*-acyl Ph-PPY* represents a significant advance in the state of the art. This work thus marks an important first step toward the development of an efficient non-enzymatic catalyst for the asymmetric acylation of amines. Ongoing investigations are focused on the discovery of acylating agents that will permit this challenging goal to be achieved.

Support has been provided by Bristol-Myers Squibb, Merck, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034), Pfizer, Pharmacia & Upjohn, and Procter & Gamble. We thank J. Craig Ruble and Beata Tao for preliminary studies.

Notes and references

1 E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430; E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 1999, **121**, 5813; T. Oriyama, Y. Hori, K. Imai and R. Sasaki, *Tetrahedron Lett.*, 1996, **37**, 8543; T. Sano, K. Imai, K. Ohashi and T. Oriyama, *Chem. Lett.*, 1999, 265; T. Kawabata, M. Nagato, K. Takasu and K. Fuji, *J. Am. Chem. Soc.*, 1997, **119**, 3169; S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **110**, 1629; G. T. Copeland, E. R. Jarvo and S. J. Miller, *J. Org. Chem.*, 1998, **63**, 6784.

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5 See: K. Kondo, T. Kurosaki and Y. Murakami, *Synlett*, 1998, 725 and references cited therein.

6 For the enantioselective acylation of secondary alcohols, see ref. 2.

7 For other processes, see: J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230; J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154; J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11 532; B. L. Hodous, J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 2637.

8 For example, with respect to the development of non-enzymatic methods for the kinetic resolution of alcohols, the discovery of effective stoichiometric reagents (D. A. Evans, J. C. Anderson and M. K. Taylor, *Tetrahedron Lett.*, 1993, **34**, 5563; E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809) preceded the discovery of effective catalysts (refs. 1 and 2).

9 The stereochemical preference of the complex appears to be the 'same', regardless of whether the substrate is an amine or an alcohol: acylated (−)-Ph-PPY* preferentially acylates (*R*)-1-phenylethylamine, and (−)-Ph-PPY*/Ac_2O preferentially acylates (*R*)-1-phenylethanol.

10 A preliminary study indicated that other *N*-acyl groups (*e.g.* pivaloyl) furnish lower enantioselectivity.

11 In contrast to our earlier papers on kinetic resolutions, in which we assessed stereoselection by focusing on the selectivity factor, in this work we have chosen to focus instead on the enantiomeric excess of the product. This is due to the fact that, because amine hydrochloride is the other product of these acylation reactions, calculation of a selectivity factor is not completely straightforward (the amine substrate is being 'consumed' both by acylation and by protonation).

12 H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.

13 We have established that at the end of a reaction we can recover Ph-PPY* in 95% yield.

Communication a908625k